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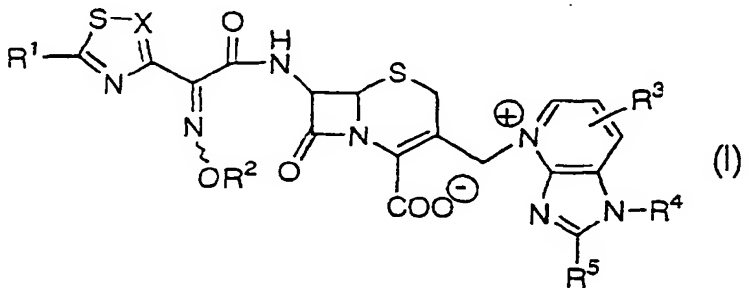
(54) IMIDAZO[4,5-b]PYRIDINIUMMETHYL-CONTAINING CEPHEM COMPOUNDS HAVING BROAD ANTIBACTERIAL SPECTRUM

(57) A cefem compound of the formula (I) shows wide antibacterial spectrum against various pathogenic bacteria including MRSA.



(I)

wherein. X is N or CY and Y is H or halogen; R^1 is amino or protected amino; R^2 is hydrogen or optionally substituted lower alkyl etc.; R^3 is hydrogen etc.; R^4 is hydrogen, optionally substituted lower alkyl, or optionally substituted N-containing heterocyclic group etc.; R^5 is hydrogen etc.; and a wavy line means syn- or anti-isomerism or a mixture thereof.

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Description

Technical Field

[0001] The present invention relates to cephem compounds having a broad antibacterial spectrum over various pathogenic bacteria and to pharmaceutical compositions containing the same. The compounds of the present invention are particularly efficacious against MRSA (methicillin resistant S. aureus).

Background Art

[0002] Study of so-called broad spectrum cephem compounds having potent antibacterial activities against various Gram-positive and Gram-negative bacteria has recently been focused on cephem compounds at which 7-side chain is substituted with aminothiazole or aminothiadiazole and 3-position with a cyclic-type quarternary ammoniummethyl group. For example, the known 7-aminothiazole types include cefepime hydrochloride (USP 4,406,899), cefpirome sulfate (USP 4,609,653, JP(A) S57-192394), and cefoselis sulfate (JP(A) H07-196665, WO97/41128), and the 7-aminothiadiazole types include cefclidin (USP 4,748,171), and cefozopran hydrochloride (USP 4,864,022, JP(A) S62-149682, JP(A) H03-47189). These cephem compounds show almost none or extremely weak activities against MRSA which has been a clinical concern.

[0003] The other documents, disclosing the same types of cephem compounds, include, for example, JP(A) 4789/1983, JP(A) 155183/1985, JP(A) 97982/1985, JP(A) 97983/1985, JP(A) 24389/1982, JP(A) 57390/1983, JP(B) 65350/1991, JP(B) 14117/1992, JP(A) 231684/1985, JP(A) 30786/1987, WO92/22556, JP(A) 222058/1993, JP(A) 157542/1994, JP(A) 101958/1995, and JP(A) 101960/1995.

[0004] Among them, JP(A) 4789/1983 discloses cephem compounds which have an optionally substituted and 2 or more N atoms- containing heterocycle cation at the 3-position. JP(A) 155183/1985 discloses cephem compounds which have a 2 or more N atoms-containing and unsaturated condensed heterocycle cation at the 3-position. These documents, however, describe or suggest no concrete embodiment of a cephem compound having an imidazopyridiniummethyl group at the 3-position.

[0005] Though JP(A) 105685/1985, equivalent to J. Med. Chem. 1990, 33, P2114-2121, discloses cephem compounds having an imidazopyridiniummethyl group at the 3-position, any of the 3-substituents of the working example compounds is limited to imidazo[4,5-c]pyridiniummethyl. On the other hand, a compound having an imidazo[4,5-b] pyridiniummethyl group at the 3- position is shown by the chemical name without any physical data or the like. Further, the [4,5-b]-type compounds have only aminothiazole group as part of the 7-side chain. Namely, the document does not concretely describe a cephem compound at which 3-position is substituted with an imidazo[4,5-b]pyridiniummethyl group and 7-side chain with aminothiadiazole.

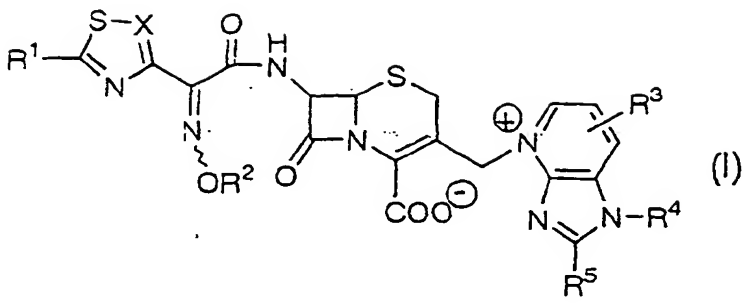
[0006] Therefore, it has been desired to develop cephem compounds of broad antibacterial spectrum which have anti-MRSA activity applicable enough to clinical use.

Disclosure of Invention

[0007] The present inventors have intensively studied to find out that introduction of an imidazo[4,5-b]pyridiniummethyl group into the 3-position of cephem compounds leads to broad antibacterial spectrum and excellent anti-MRSA activity, and have accomplished the present invention shown below.

(1) a compound of the formula(I):

[0008]



wherein,

X is N or CY and Y is H or halogen;
R^1 is amino or protected amino;
R^2 is hydrogen, optionally substituted lower alkyl or optionally substituted cycloalkyl;
R^3 is hydrogen, hydroxy, halogen, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted lower alkylthio or optionally substituted amino;
R^4 is hydrogen, hydroxy, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted cycloalkyl, optionally substituted cycloalkyl(lower)alkyl or an optionally substituted N-containing heterocyclic group;
R^5 is hydrogen, amino, optionally substituted lower alkyl, optionally substituted lower alkoxy or optionally substituted lower alkylthio, or R^4 and R^5 taken together may form lower alkylene in which an optional hetero atom(s) intervene; and
a wavy line means syn- or anti-isomerism or a mixture thereof, an ester, a pharmaceutically acceptable salt, a prodrug, or a solvate thereof (herein after may be referred to as compound (I)).
(2) the compound described in above (1) wherein X is N.
(3) the compound described in above (1) wherein R^1 is amino.
(4) the compound described in above (1) wherein R^2 is hydrogen or optionally substituted lower alkyl.
(5) the compound described in above (4) wherein R^2 is lower alkyl optionally substituted with halogen.
(6) the compound described in above (1) wherein R^3 is hydrogen.
(7) the compound described in above (1) wherein R^4 is hydrogen, optionally substituted lower alkyl or an optionally substituted N-containing heterocyclic group.
(8) the compound described in above (7) wherein R^4 is hydrogen, lower alkyl optionally substituted with amino, lower alkylamino or hydroxy(lower) alkylamino, or an optionally substituted 4- to 6-membered N-containing saturated heterocyclic group.
(9) the compound described in above (1) wherein R^5 is hydrogen.
(10) the compound described in above (1) wherein the wavy line means syn-isomerism.
(11) the compound described in above (1) wherein X is N; R^1 is amino; R^2 is hydrogen or optionally substituted lower alkyl; R^3 is hydrogen; R^4 is hydrogen, optionally substituted lower alkyl or an optionally substituted N-containing heterocyclic group; R^5 is hydrogen; and the wavy line means syn-isomerism.
(12) the compound described in above (11) wherein X is N; R^1 is amino; R^2 is hydrogen or lower alkyl optionally substituted with halogen; R^3 is hydrogen; R^4 is hydrogen, lower alkyl optionally substituted with amino, lower alkylamino or hydroxy(lower)alkylamino, or an optionally substituted 4- to 6-membered N-containing saturated heterocyclic group; R^5 is hydrogen; and the wavy line means syn-isomerism.
(13) the compound described in above (12) wherein X is N; R^1 is amino; R^2 is hydrogen, $-CH_3$, $-CH_2F$, $-CH_2CH_3$ or $-CH_2CH_2F$; R^3 is hydrogen; R^4 is hydrogen, $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-(CH_2)_3NH_2$, $-(CH_2)_3NHCH_3$, $-(CH_2)_3NH(CH_2)_2OH$, azetidinyl, pyrrolidinyl or piperidyl; R^5 is hydrogen; and the wavy line means syn-isomerism.
(14) the compound described in above (13) wherein X is N; R^1 is amino; R^2 is hydrogen, $-CH_2F$ or $-CH_2CH_3$; R^3 is hydrogen; R^4 is hydrogen, $-(CH_2)_3NH_2$, $-(CH_2)_3NHCH_3$ or $-(CH_2)_3NH(CH_2)_2OH$; R^5 is hydrogen; and the wavy

line means syn-isomerism.

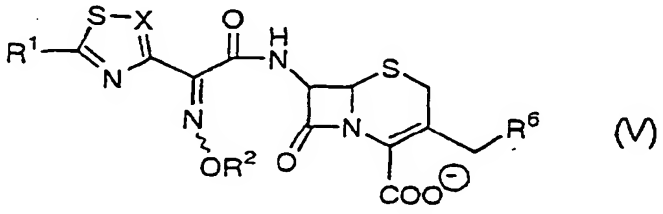
(15) the compound described in above (14), a pharmaceutically acceptable salt or hydrate thereof wherein X is N; R^1 is amino; R^2 is $-CH_2F$; R^3 is hydrogen; R^4 is $-(CH_2)_3NHCH_3$; R^5 is hydrogen; and the wavy line means syn-isomerism.

(16) the compound described in above (15) which is a sulfate or a hydrate thereof.

(17) the compound described in any of above (1) to (16), which shows an antibacterial activity against Gram-positive bacteria including MRSA and Gram-negative bacteria.

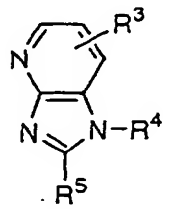
(18) the compound described in (17) of which MIC_{50} value against MRSA is 50 μg/ml or less.

(19) A method for preparing the compound described in any of above (1) to (18), which comprises reacting a compound of the formula(V):



(V)

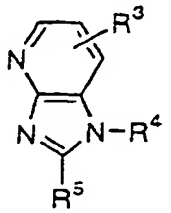
wherein R^6 is a leaving group and the other symbols are the same as defined above, an ester, or a salt thereof with a compound of the formula(IV):



(IV)

wherein each symbol is the same as defined above, followed by optional deprotection.

(20) a compound of the formula(IV):



(IV)

wherein each symbol is the same as defined above.

(21) the compound described in above(20) wherein R^3 is hydrogen; R^4 is $(CH_2)_3NR^aCH_3$ wherein R^a is H or an amino-protecting group; and R^5 is hydrogen,

(22) a pharmaceutical composition which contains a compound described in any of above (1) to (18).

(23) a composition for use as an antibacterial agent which contains a compound described in any of above (1) to (18).

(24) a method for preventing or treating bacterial infectious diseases, which comprises administering a compound described in any of above (1) to (18).

(25) use of the compound described in any of above (1) to (18) for preparing a composition for use as an antibacterial agent.

Best Mode for Carrying Out the Invention

[0009] Terms used herein are explained below. Unless otherwise mentioned, each term, by itself or as part of another, has a common meaning.

(Definition of X)

[0010] X is preferably N or CH, and more preferably N. Examples of halogen shown by Y include F, Cl, and Br and preferred is Cl.

(Definition of R^1)

[0011] The protecting group of protected amino may be that known in the present field, such as C1~C6 alkanoyl (e.g., formyl, acetyl, propionyl, butyryl, valeryl, pivaroyl, and succinyl), C3~C5 alkenoyl (e.g., acryloyl, crotnoyl, and cinnamoyl), C6~C10 arylcarbonyl (e.g., benzoyl, naphthoyl, p-toluoyl, and p-hydroxybenzoyl), heterocyclylcarbonyl group (example of the heterocyclyl: e.g., 2-pyrrolyl, 3-pyrazolyl, 4-imidazolyl, 1,2,3-triazolyl, 1H-tetrazolyl, 2-furyl, 3-thienyl, 4-oxazolyl, 3-isooxazolyl, 2-pyrrolidinyl, 3-pyridyl, and 4-pyridazinyl), C1~C6 alkylsulfonyl (e.g., methanesulfonyl and ethanesulfonyl), C6~C10 arylsulfonyl (e.g., benzenesulfonyl, naphthalenesulfonyl, and p-toluenesulfonyl), substituted oxycarbonyl (e.g., methoxymethyloxycarbonyl, acetylmethyloxycarbonyl, 2-trimethylsilylethoxycarbonyl, 2-methanesulfonylethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-cyanoethoxycarbonyl, p-methylphenoxycarbonyl,p-methoxyphenoxycarbonyl,p-chlorophenoxycarbonyl, benzyloxycarbonyl, p-methylbenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, t-butoxycarbonyl (Boc), and 2-propenyloxycarbonyl), substituted silyl (e.g., trimethylsilyl and tertbutyldimethylsilyl), and optionally substituted aralkyl (e.g., p-methoxybenzyl (PMB) and benzhydryl (BH)). One or two of the protecting group, preferably one, may bond to an amino group. A preferred R^1 is amino in the light of the antibacterial activity.

(Definition of R^2)

[0012] Lower alkyl includes a straight or branched C1 to C6 alkyl such as methyl, ethyl, n-propyl, i-propyl, t-butyl, n-pentyl, and n-hexyl, and preferred is C1 to C3 alkyl, more preferred is methyl, ethyl or n-propyl.

[0013] Cycloalkyl includes C3 to C7 cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

[0014] When the above lower alkyl or cycloalkyl is substituted, examples of the substituent include halogen (e.g., F, Cl, and Br), hydroxy, carboxy, cyano, amino, carbamoyloxy, sulfamoyl, lower alkoxycarbonyl (e.g., methoxycarbonyl, and ethoxycarbonyl), lower alkylthio (e.g., methylthio, and ethylthio), and preferred is halogen, esp., F. The number of the substituent is one or more.

[0015] Preferable R^2 includes hydrogen and optionally substituted lower alkyl (e.g., CH_3, CH_2F, CH_2CH_3, and CH_2CH_2F), and more preferred is lower alkyl substituted with halogen (e.g., CH_2F). The wavy line of "-OR2" preferably means syn-isomerism for the 7-amido bond part.

(Definition of R^3)

[0016] Examples of halogen include F, Cl, Br and I.

[0017] Examples of lower alkyl include the above lower alkyl defined for R^2, and preferred is methyl.

[0018] Examples of lower alkoxy include oxy bonding to lower alkyl, such as methoxy, ethoxy, n-propoxy, i-propoxy, t-butoxy, n-pentyloxy, and n-hexyloxy.

[0019] Examples of lower alkylthio include thio bonding to the lower alkyl, such as methylthio, ethylthio, n-propoxy, i-propylthio, t-butylthio, n-pentylthio, and n-hexylthio.

[0020] When the above lower alkyl, lower alkoxy or lower alkylthio is substituted, examples of the substituent include halogen (e.g., F, Cl, and Br), hydroxy, carboxy, cyano, amino, carbamoyloxy, sulfamoyl, lower alkoxycarbonyl (e.g., methoxycarbonyl and ethoxycarbonyl), and lower alkylthio (e.g., methylthio and ethylthio).

[0021] Examples of the substituent of "optionally substituted amino" include the above-described lower alkyl (e.g., methyl and ethyl) and the above-described amino-protecting group, and one or two of the substituents may be located on the amino.

[0022] R_3 may be located at any of the 2- to 4- positions of the pyridinium ring. R_3 is preferably hydrogen.

(Definition of R^4)

[0023] Lower alkyl and cycloalkyl are the same as the above-described lower alkyl and cycloalkyl, respectively, which are defined for R^2. Cycloalkyl(lower)alkyl means lower alkyl bonding to the cycloalkyl, such as cyclopropylmethyl, 1-cyclopropylethyl, 3-cyclopropylpropyl, cyclobutylmethyl, cyclopentylethyl and 3-cyclohexylpropyl.

[0024] Examples of lower alkenyl include a straight or branched C2 to C6 alkenyl, such as vinyl, aryl, 1-propenyl, i-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyll-propenyl, 2-methyl2-propenyl, 1-pentenyl, and 2-hexenyl, and preferred is aryl.

[0025] Lower alkoxy is the same as the above-described lower alkoxy defined for R^3.

[0026] When each of the above lower alkyl, lower alkenyl, lower alkoxy, cycloalkyl and cycloalkyl(lower)alkyl is substituted, examples of the substituent include one or more, same or different, group(s) selected from hydroxy, optionally substituted carbamoyl (wherein the substituent is methyl; ethyl, propyl or $-(CH_2)_3CH(NH_2)CONH_2$), halogen (e.g, F and Cl), $CO(CH_2)nCH(NH_2)CONH_2$ (n=1 to 3), optionally substituted amino wherein the substituent is lower alkyl (e.g., methyl, ethyl, and propyl), lower alkenyl (e.g., aryl), cycloalkyl (e.g., cyclopropyl), lower alkoxycarbonyl (e.g., t-butoxycarbonyl), hydroxy(lower)alkyl (e.g., hydroxymethyl, 1-hydroxyethyl, and 2-hydroxyethyl), sulfonic acid-oxy(lower)alkyl (e.g., 2-sulfonic acid-oxyethyl) or amino(lower)alkyl (e.g., 2-aminoethyl)), lower alkoxy (e.g., methoxy, ethoxy, and propoxy), lower alkoxycarbonyl (e.g., methoxycarbonyl and ethoxycarbonyl), and N-containing heterocyclic group which is mentioned below wherein preferable is azetidinyl, pyrrolidinyl, piperidinyl, pyridyl or the like.

[0027] The N-containing heterocyclic group means an aromatic or non-aromatic heterocyclic group which contains at least one or more N atom(s) and optional O or S atom(s), such as azetidinyl, pyrrolidinyl, piperidinyl, imidazolydinyl, pyrazolidinyl, piperazinyl, thiazolidinyl, oxazolidinyl, morpholinyl, thio morpholinyl, thiazolinyl, oxazolinyl, imidazolinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isooxazolyl, thiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, imidazolyl, triazolyl, and tetrazolyl. Preferred is a non-aromatic group, esp., a 4- to 6-membered N-containing saturated heterocyclic group such as azetidinyl (e.g., 3- azetidinyl), pyrrolidinyl (e.g., 3- pyrrolidinyl), and piperidinyl (e.g., 4-piperidinyl).

[0028] When the heterocyclic group is substituted, examples of the substituent include one or more of the same or different group(s) selected from halogen (e.g., F and Cl), hydroxy, hydroxy(lower)alkyl (e.g., hydroxymethyl, 1-hydroxyethyl, and 2-hydroxyethyl), optionally substituted amino (wherein the substituent is lower alkyl (e.g., methyl, ethyl, and propyl) or the like), optionally substituted carbamoyl (wherein the substituent is e.g., methyl and ethyl), lower alkyl (e.g., methyl and ethyl), lower alkoxy (e.g., methoxy, ethoxy, and propoxy), imino(lower) alkyl (e.g., iminomethyl and 1-imonoethyl), halogenated(lower)alkyl (e.g., trifluoromethyl), optionally esterfied carboxy, cyano, nitro, lower alkylthio (e.g., methylthio), lower alkoxyalkoxy (e.g., methoxymethoxy and ethoxyethoxy), lower alkoxycarbonyl (e.g., methoxycarbonyl and ethoxycarbonyl), acylamino (e.g., acetylamino) and the like. In addition to those, the possible substituents on the N atom of the heterocyclic group include the above-described amino-protecting group.

[0029] R^4 is preferably one, two or more of the same or different group(s) selected from hydrogen, optionally substituted(lower)alkyl (wherein the substituent is preferably optionally substituted amino (wherein the substituent is lower alkyl (e.g., methyl), hydroxy(lower)alkyl (e.g., 2-hydroxyethyl), sulfonic acid-oxy(lower)alkyl (e.g., 2- sulfonic acid-oxyethyl) or the like), lower alkoxycarbonyl (e.g., t-butoxycarbonyl), carbamoyl, lower alkylcarbamoyl(e.g., methylcarbamoyl), hydroxy, halogen, lower alkoxy (e.g., methoxy), the above-described amino-protecting group (e.g., Boc, PMB) or the like), N-containing heterocyclic group and the like, more preferably hydrogen, $-CH_3$, $-CH_2CH_3$, $(CH_2)_2CH_3$, $-(CH_2)_3NH_2$, $-(CH_2)_3NHCH_3$, $-(CH_2)_3NH(CH_2)_2OH$, azethidinyl, pyrrolidinyl or piperidinyl, and most preferably hydrogen, $-(CH_2)_3NH_2$, $(CH_2)_3NHCH_3$ or $-(CH_2)_3NH(CH_2)_2OH$.

(Definition of R^5)

[0030] The lower alkyl, by itself or as part of lower alkylthio, is the same as that defined for R^2. The lower alkoxy is the same as that defined for R^3.

[0031] Examples of the substituent on the lower alkyl, lower alkoxy or lower alkylthio include halogen (e.g., F, Cl, and Br), hydroxy, carboxy, cyano, amino, carbamoyloxy, sulfamoyl, lower alkoxycarbonyl (e.g., methoxycarbonyl and ethoxycarbonyl), lower alkylthio(e.g., methylthio and ethylthio) and the like.

[0032] R^5 is preferably hydrogen, methyl, methylthio or the like, and more preferably hydrogen.

[0033] R^4 and R^5 taken together may form lower alkylene in which an optional hetero atom(s) intervene. When the hetero atom is N, it may be substituted with lower alkyl or the like, resulting in that R^4 and R^5 taken together forms $-(CH_2)_3$-N(Me)- for example.

[0034] The esters of compound (I) include an ester which is formed at the 4-carboxy part, e.g., an ester useful as an intermediate or a metabolic ester. Examples of the ester-residue include e.g., optionally substituted C1-C6 alkyl, C2-C6 alkenyl, C3-C10 cycloalkyl, C3-C10 cycloalkyl(C1-C6)alkyl, optionally substituted C6-C10 aryl, optionally substituted C7-C12 aralkyl, di(C6-C10)arylmethyl, tri(C6-C10)arylmethyl, and substituted silyl.

[0035] Examples of the optionally substituted C1-6 alkyl include e.g., methyl, ethyl, n-propyl, n-butyl, t-butyl, n-pentyl, and n-hexyl, each may be substituted with benzyloxy, C1-4 alkylsulfonyl (e.g., methanesulfonyl), trimethylsilyl, halogen (e.g., F, Cl, and Br), acetyl, nitrobenzoyl, mesylbenzoyl, phthalimide, succinoylimide, benzenesulfonyl,phenylthio, di-C1-4alkylamino (e.g., dimethylamino), pyridyl, C1-4alkylsulfinyl (e.g., methanesulfinyl), cyano and the like. Such substituted C1-6 alkyl include e.g., benzyloxymethyl, 2-methane sulfonylethyl, 2-trimethylsilylethyl, 2,2,2-trichloroethyl, 2-iodoethyl, acetylmethyl, p-nitrobenzoylmethyl, p-mesylbenzoylmethyl, phthalimidemethyl, succinoylimidemethyl, benzenesulfonylmethyl, phenylthiomethyl, and 1-dimethylaminoethyl. The above C2-6 alkenyl includes e.g., vinyl, aryl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 1,1-dimethylaryl, 3-methyl and 3-butenyl. The above C3-10 cycloalkyl includes e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and adamantyl. The above C3-10 cycloalkyl(C1-6)alkyl includes e.g., cyclopropylmethyl, cyclopentylmethyl, and cyclohexylmethyl. The above C6-10 aryl includes e.g., phenyl, α-naphthyl, β-naphthyl, and biphenyl, each may be substituted with nitro, halogen (e.g., F, Cl, and Br) or the like, and such substituted aryl includes e.g., p-nitrophenyl and p-chlorophenyl. The above optionally substituted C7-12 aralkyl includes e.g., benzyl, 1-phenylethyl, 2-phenylethyl, phenylpropyl and naphthylmethyl, each may be substituted with nitro, C1-4 alkoxy (e.g., methoxy), C1-4 alkyl (e.g., methyl, ethyl), hydroxy or the like. Such substituted group is exemplified by p-nitrobenzyl, p-methoxybenzyl (PMB), or 3,5-di-t-butyl-4-hydroxybenzyl. The above di(C6-10 aryl)methyl includes benzhydryl and the C6-10 arylmethyl includes trityl, and the substituted silyl includes trimethylsilyl and tert-butyldimethylsilyl, for example.

[0036] Examples of the pharmaceutically acceptable salt of compound (I) include salts formed with inorganic bases, ammonia, organic bases, inorganic acids, organic acids, basic amino acids, halogen ions or the like, and inner salts. Examples of the inorganic base include alkali metal (e.g., Na and K) and alkaline earth metal (e.g., Mg). Examples of the organic base include procaine, 2-phenylethylbenzylamine, dibenzylethylenediamine, etanolamine, di etanolamine, tris(hydroxymethyl)aminomethane, polyhydroxyalkylamine, and N-methyl glucosamine. Examples of the inorganic acid include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, and phosphoric acid. Examples of the organic acid include p-toluene sulfonic acid, methane sulfonic acid, formic acid, trifluoroacetc acid and maleic acid. Examples of the basic amino acid include lysine, arginine, ornithine and histidine. The quarternary ammonium cation on the 3-side chain of compound (I) may form an inner salt with the 4-COO group as a counter ion. When the group at the 4-position is COOH or COOR wherein R is a metal cation or ester-residue, the quarternary ammonium cation is combined with a counter ion. Compound (I) is preferably an inorganic salt, more preferably a salt of sulfuric acid, and most preferably mono sulfate in the light of the crystallinity, conservation stability, handling in pharmaceutical manufacturing or the like.

[0037] Prodrug means a derivative of compound(I), which has a chemically or metabolically decomposable group and is converted to a pharmaceutically active compound (I) by solvolysis or under physiological conditions in vivo. A method for selecting and preparing an appropriate prodrug-derivative is described in e.g., Design of Prodrugs, Elsevier, Amsterdam 1985.

[0038] When compound (I) has a carboxy group, examples of the prodrug include an ester derivative prepared by reacting an acidic original compound with a proper alcohol or an amide derivative prepared by reacting an acidic original compound with a proper amine. Preferred esters as the prodrug include methyl ester, ethyl ester, n-propyl ester, isopropyl ester, n-butyl ester, isobutyl ester, tert-butyl ester, and morpholinoethylester. When compound (I) has a hydroxyl group, examples of the prodrug include an acyloxy derivative which is prepared by reacting a hydroxyl group-containing compound with a proper acyl halide or acid anhydride. Preferred acyloxy includes $-OCOC_2H_5$, -OCO(t-Bu), $-OCOC_{15}H_{31}$, -OCO(m-COONa-Ph), $-OCOCH_2CH_2COONa$, $-OCOCH(NH_2)CH_3$ and $-OCOCH_2N(CH_3)_2$. When compound (I) has an amino group, examples of the prodrug include an amide derivative which is prepared by reacting an amino group-containing compound with a proper halogenated acid or mixed acid anhydride. Preferred amides include $-NHCO(CH_2)_{20}CH_3$, $-NHCOCH(NH_2)CH_3$ and the like.

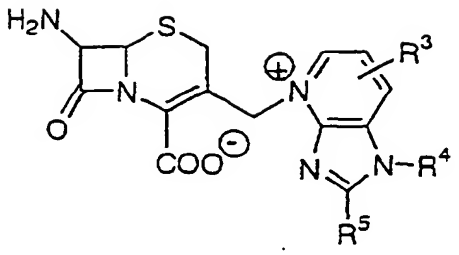
[0039] The solvate of compound (I) is preferably hydrate e.g., 0.5- to 10- hydrate, and more preferably 4-, 5-, 6-, 7-, or 8-hydrate. Particularly preferred is a crystalline monosufate 4- to 8-hydrate. Compound (I) may be a solvate formed with i-propanol, ethanol, trifluoroacetic acid or the like.

[0040] Compound (I) is preferably a compound described in any of above (11) to (18), more preferably a compound (I) wherein X is N; R^1 is amino; R^2 is $-CH_2F$; R^3 is hydrogen; R^4 is $-(CH_2)_3NHCH_3$; R^5 is hydrogen; and the wavy line means syn-isomerism or a salt thereof, esp. mono sulfate, for example. Among the sulfate, crystals are preferred to non-crystals in the light of their stability for pharmaceutical preparation or the like. and more preferred are crystalline hydrates such as 4- to 7- or 8-hydrate of monosulfate, esp. the 4- or 5-hydrate. These crystals are characterized by specific main peaks of the powder X-ray diffractometry.

[0041] Methods for preparing compound (I) are shown below.

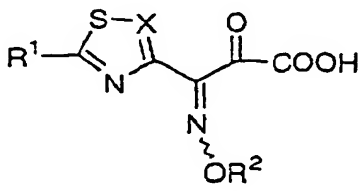
(Method 1)

[0042] Compound (I) can be synthesized by reacting a 7-amino compound of the formula (II):



(II)

wherein each symbol is the same as defined above, a ester or salt thereof (each hereinafter referred to as compound (II)) with a carboxylic acid of the formula(III):



(III)

wherein each symbol is the same as defined above, or a reactive derivative thereof (each hereinafter referred to as compound (III)).

[0043] Examples of the ester or salt of compound (II) include the same as those mentioned for compound (I).

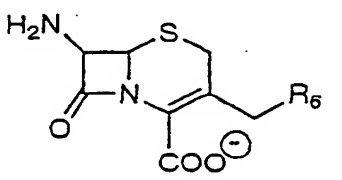
[0044] Examples of the reactive derivative of compound (III) include inorganic base salts, organic base salts, acid halides, acid azides, acid anhydrides, mixed acid anhydride, active amide, active ester, active thioester. The inorganic base includes alkaline metals (e.g., Na and K) and alkaline earth metals (e.g., Ca and Mg); The organic base includes trimethylamine, triethylamine, tert-butyldimethylamine, dibenzylmethylamine and benzyldimethylamine; the acid halide includes acid chloride and acid bromide; the mixed acid anhydride includes mixed monoalkylcarboxylic acid anhydride, mixed alphatic carboxylic acid anhydride, aromatic carboxylic acid anhydride, oraganic sulfonic acid anhydride, the active amide includes amide formed with heterocyclic compound containing N atom, for example. Examples of the active ester include organic phosphate esters (e.g., diethoxy phosphate ester and diphenoxy phosphate ester), p-nitrophenyl ester, 2,4-dinitrophenyl ester, cyanomethyl ester, and the active thioester includes esters formed with aromatic heterocyclicthio compound (e.g., 2-pyridilthio ester).

[0045] The above reaction may be carried out using an appropriate condensing agent, if necessary. Examples of the condensing agent include e.g., N,N'-dicyclohexylcarbodiimide, N,N'-carbonyldiimidazole, N,N'-thiocarbonyldiimidazole, N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, phosphorus oxychloride, alkoxyacetylene, 2-chloropyridiniummethyl iodine, and 2-fluoropyridiniummethyl iodine.

[0046] Examples of solvents used in the reaction include ethers (e.g., dioxane, THF, diethylether, tert-butylmethylether, and diisopropylether), esters (e.g., ethyl formate, ethyl acetate, and n-butyl acetate), halogenated hydrocarbons (e.g., dichloromethane, chloroform, and carbon tetrachloride), hydrocarbons (e.g., n-hexane, benzene, and toluene), amides (e.g., formamide, N,N-dimethylformamide (DMF), N,N-dimethylacetoamide, and N-methylpyrrolidone), ketones (e.g., acetone and methylethylketone), nitryls (e.g., MeCN and propionitryl), dimethylsulfoxide, and water.

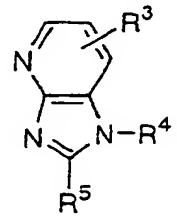
[0047] The amount of compound (III) is usually about 1 - 5 mol, preferably about 1 - 2 mol, per compound (II) 1 mol. The reaction may be carried out at about -80 to 80°C, preferably about -40 to 50°C.

[0048] Compound (II) is prepared, for example, by reacting a compound of the formula (II'):



(II')

wherein R^6 is a leaving group (e.g., hydroxy, halogen (e.g., Cl, Br, I), carbamoyloxy, substituted carbamoyloxy, and acyloxy), an ester or salt thereof (hereinafter referred to as compound (II')) with an imidazo[4,5-b]pyridine compound of the formula (IV):



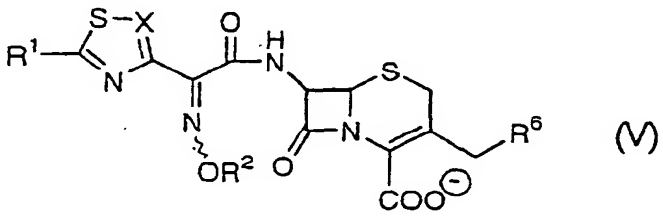
(IV)

wherein each symbol is the same as defined above, or a salt thereof (hereinafter referred to as compound(IV)).

[0049] Compound (II') may be prepared according to documents (e.g., JP(A) 60-231684 and JP(A) 62-149682). Examples of the acyloxy in R^6 include acetoxy, chloroacetoxy, propionyloxy, butylyloxy, pivaloyloxy, and 3-oxobutylyloxy. Examples of above substituted carbamoyloxy include methylcarbamoyloxy and N,N-dimethylcarbamoyloxy. Examples of the salt of compound (IV) include inorganic acid addition salts (e.g., hydrochloride, hydrobromate, sulfate, nitrate, and phosphate) and organic acid addition salts (e.g., formate, acetate, trifluoroacetate, methanesulfonate, and p-toluenesulfonate).

(Method 2)

[0050] Compound (I) is prepared by reacting a compound of the formula (V):



(V)

wherein each symbol is the same as defined above, an ester or salt thereof (hereinafter referred to as compound (V)) with the above-described compound (IV).

[0051] Examples of salts or esters of the compound (V) are the same as those of compound (I).

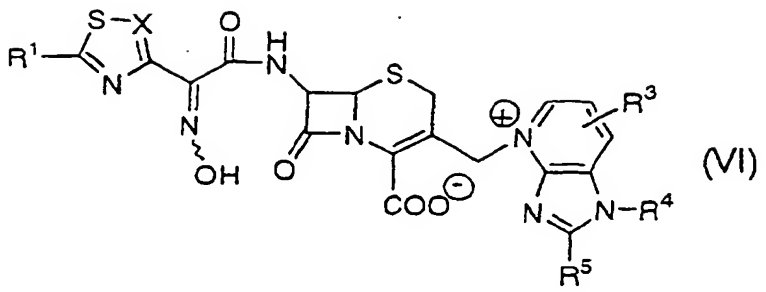
[0052] Examples of solvents used in the reaction are the same as those used in the above-described Method (1). In addition, compound (IV) may be used also as a solvent.

[0053] The amount of compound (IV) is usually about 1 - 5 eq. mol, preferably about 1 - 3 eq. mol, per compound (V). The reaction is usually conducted at about 0 - 100°C, preferably about 10 - 80°C, within several minutes to several hours.

[0054] In the process, a reaction mediator mat be added, such as iodides (e.g., NaI and KI) and thiocyanate (e.g., sodium thiocyanate and potassium thiocyanate). When R^6 is hydroxy, the reaction may be conducted in the presence of various phosphorus compounds according to JP(A) Kokai S58-43979.

(Method 3)

[0055] Compound (I), provided R^2 is not hydrogen, can be obtained by reacting a compound of the formula(VI):



(VI)

wherein each symbol is the same as above, an ester or, a salt thereof (hereinafter referred to as compound(VI)) with a compound of the formula: R^2OH wherein R^2 is the same as above, or a reactive derivative thereof. The reactive derivative of R^2OH includes a compound of the formula: R^2Z wherein Z is a leaving group such as halogen, methanesulfonyloxy, and benzenesulfonyloxy.

(3-1) reaction using R^2OH

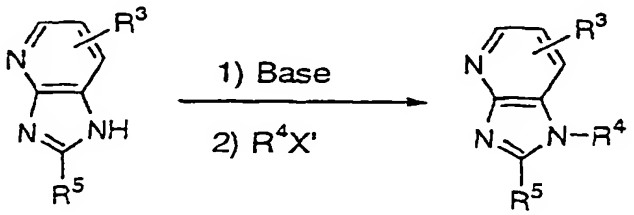
[0056] Compound (VI) and R^2OH are reacted in the presence of an appropriate dehydrating agent. Examples of the dehydrating agent include phosphorus oxychloride, thionyl chloride, dialkyl azodicarboxylate/phosphine, and N,N'-dicyclohexylcarbodiimide. The reaction solvate includes e.g., the above-described ethers and hydrocarbons. The amount of compound R^2OH is usually about 1 to 1.5 mol per compound (VI) 1 mol. The reaction temperature is usually about 0 to 50°C.

(3-2) reaction using R^2Z

[0057] R^2Z and compound (VI) are reacted, if necessary, in the presence of a base. The reaction solvates include e.g., the above-described ethers, esters, halogenated hydrocarbons, hydrocarbons, amides, ketones, nitryls, alcohols, and water. The base includes for example, alkali metal salt (e.g., Na_2CO_3, $NaHCO_3$, K_2CO_3), alkali metal hydroxide (e.g., NaOH, KOH). The amount of R^2Z is usually about 1 to 5 mol per compound(VI) 1 mol. The reaction temperature is about -30 to 100°C, preferably about 0 to 80°C. The above-described compound (IV) is known or new. Even when the compound (IV) is new, it can readily be synthesized through reactions well known to a person skilled in the art. A representative method is shown below.

(Method A)

[0058]

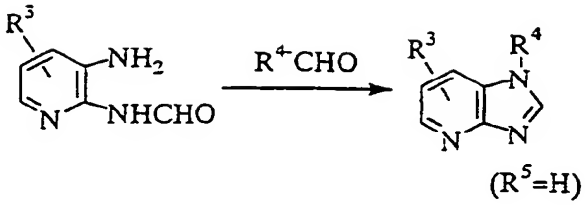


(VII) (IV)

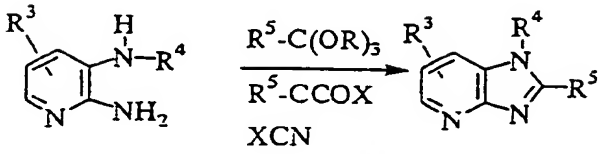
[0059] Compound (IV) can be prepared by reacting compound (VII) with R^4X' (R^4 is the same as defined above, provided R^4 is not H. X' is a leaving group (e.g., Iodine and methanesulfonyloxy)) in the presence of a base (e.g., NaH and $CsCO_3$). The reaction can also be conducted under Mitsunobu's reaction condition: R^4OH / dialkyl axodicarboxylate / phosine. The reaction solvates include e.g., the above-described ethers and amides. The reaction temperature is about -20 to 150°C, preferably about 0 to 50°C.

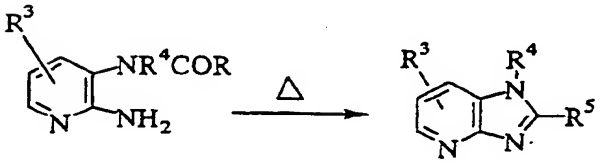
[0060] The obtained compound (IV) may further be chemically modified to other compounds. Other methods B to F

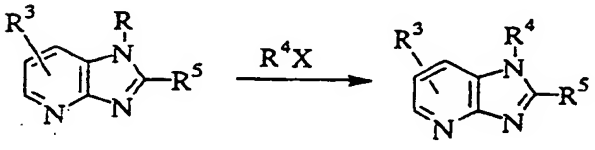
are shown below.

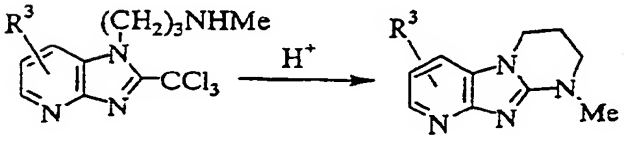
B 

(R^5=H)

C 

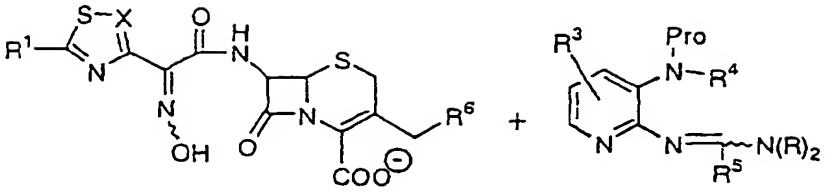
D 

E 

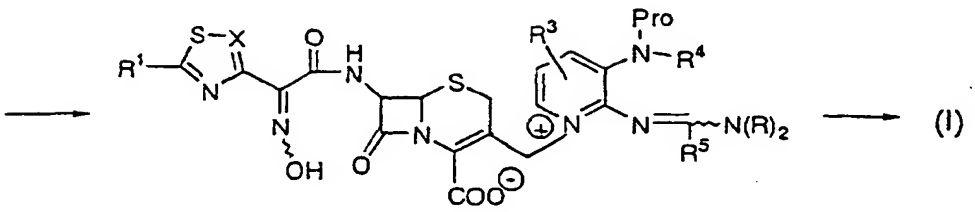
F 

(X=Halogen, R=organic residue)

(Method 4)



(V) (VIII) (Pro=N-protecting group, R=lower alkyl etc.)



(IX)

(wherein each symbol is the same as defined above)

[0061] Compound (V) and pridine derivative (VIII) are reacted to give compound (IX) (Step 1), then which is cyclized at the 3-side chain portion (Step 2), to give compound (I) (see, Reference Examples 31 to 33 and Examples 29 to 32.)

[0062] Step 1 reaction may be carried out according to the above Method 2. The 4-carboxy group of compound (IX) may be protected when N^+ of the 3-side chain is combined with a counter ion. The cyclization of Step 2 is preferably conducted in the presence of an acid. Examples of the acid include inorganic acids (e.g., HCl, H_2SO_4, H_2PO_3, HNO_3, toluene sulfonate, and methane sulfonate) and organic acids (e.g., HCO_2H and CH_3CO_2H). Preferred is H_2SO_4 for the yield, handling or the like. The temperature of the acid-treating reaction is about -20 to about 100°C, preferably about 0 to about 30°C, and the reaction time is several minutes to several hours. The reaction solvates include acetic acid, ethyl acetate, acetonitrile, acetone, dimethylformamide (DMF), and tetrahydrofuran (THF). In a preferred embodiment of the Step 2 cyclization, the amino-protecting group (e.g., PMB and Boc) or 4-carboxy-protecting group (e.g., PMB) of compound (IX) can be deprotected.

[0063] Prior to the above each reaction, a functional group such as amino, imino, hydroxy, and carboxy may be protected by a method well known to skilled persons and if necessary deprotected after the reaction.

[0064] Compound (I) shows a broad antibacterial spectrum and so it can be used for preventing or treating mammals (e.g., humans) for various diseases caused by pathogenic microorganisms, such as respiratory tract infection and genito-urinary tract infection. The characters of compound (I) include the following points:

(1) excellent activity against Gram-negative bacteriums
(2) excellent activity against Gram-positive bacteriums
(3) excellent activity against methicillin-resistant S. aureus (MRSA)
(4) excellent activity against Pseudomonas
(5) excellent in vivo dynamics: high blood drug concentration, long time action, and good tissue transplantatio; compound (I) is not liable to be metabolized, thus the urinary recovery of the non-metabolite is high.
(6) excellent in water-solubility and safety

[0065] Compound (I) can be orally or parenterally administered in a form of injection, capsule, granule, or the like, and a preferred form is injection. The daily dosage can usually be varied in the range of about 0.1 to 100 mg/kg, preferably about 0.5 to 50 mg/kg, which is administered in two to four divisions if necessary. The pharmaceutically acceptable carriers used to injections include e.g., distilled water, physiologic saline, and pH adjusting agents such as bases. For preparing capsules, granules, and tables, other pharmaceutically acceptable carriers can be used, such

as excipients (e.g., starch, lactose, sucrose, calcium carbonate, calcium phosphate), binders (e.g., starch, Arabian gum, carboxymethyl cellulose, hydroxypropyl cellulose, crystalline cellulose), and lubricants (e.g., magnesium stearate, talc).

[0066] Examples are shown below.

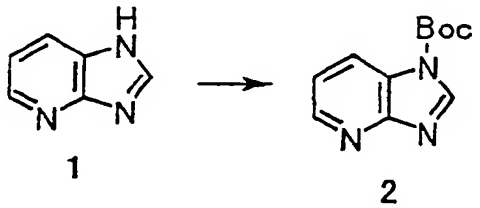
(abbreviation)

[0067]

HP-20=HP-20SS (Daiya ion exchange resin, Mitsubishikagaku);
Me=metyl; Et=ethyl; i-Pr=isopropyl; t-Bu=tert-butyl MeOH=methanol; EtOH=ethanol; i-PrOH=isopropanol; AcOH=acetic acid;
AcOEt=ethyl acetate; Et_2O=diethylether; MeCN=acetonitrile; $MeNO_2$=nitromethane; DMF=dimethylformamide; THF=tetrahydrofuran; Boc=t-butoxycarbonyl; PMB = p-methoxybenzyl; BH = benzhydryl; Ms = methanesulfonyl

Reference Example 1

[0068]

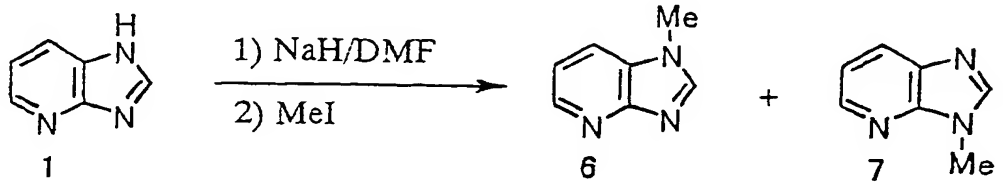


1 2

[0069] To a solution of compound 1 (Aldrich, 1 775 mg, 6.5 mmol) in DMF 8 ml, was added di-tert-buthyl dicarbonate (hereinafter referred to as "$(Boc)_2O$") (1.65 ml, 1.1eq) under ice-cooling and the mixture was allowed to stand at room temperature over night. The reaction mixture was evaporated under reduced pressure and the obtained oily residue was purified with silica gel chromatograph to give compound 2 (1.16 g, 81%).
^{1}H-NMR ($CDCl_3$) δ: 1.71 (9H, s), 7.32 (1H, dd, J = 4.8, 8.1 Hz), 8.28 (1H, dd, J = 1.8 , 8.1 Hz), 8.62 (1H, dd, J = 1.8, 4.8 Hz), 8.66 (1H, s).
IR (Nujole) cm^{-1}: 3136, 2979, 2853, 1761, 1744, 1606, 1577, 1531, 1506, 1403, 1370, 1156, 781.
Elementary Analysis as $C_{11}H_{13}N_3O_2 \cdot 0.1\ H_2O$ calc.: C,59.77 ; H,6.02 ; N,19.01
found: C,59.55 ; H,6.03 ; N,19.35 (%)

Reference Example 2

[0070]



1 6 7

[0071] To a solution of compound 1 (Aldrich, 920 mg, 7.72 mmol) in THF 45 ml, was added 60% NaH (340 mg, 1.1eq) under ice-cooling and the mixture was stirred at room temperature to 45°C for 1 hr, then MeI (0.53 ml, 1.1eq) was added thereto under ice-cooling at room temperature and the resultant mixture was allowed to stand over night. The reaction mixture was evaporated under reduced pressure and water and AcOE were added thereto, then the water layer was subjected to purification with HP-20 chromato, to give compound 6 (728 mg, 70.8 %), then compound 7 (125 mg, 12 %).

(compound 6)

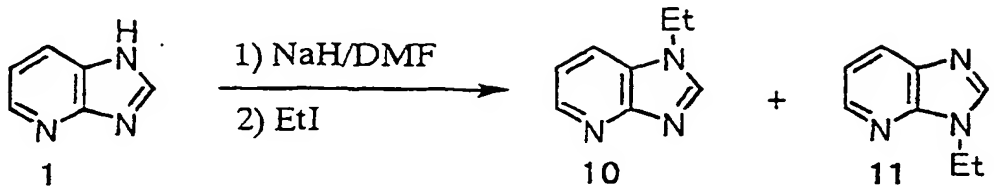
[0072] ^{1}H-NMR ($CDCl_3$) δ: 3.87 (3H, s). 7.23 (1H, dd, J = 5.1, 8.1 Hz), 7.68 (1H, dd, J = 1.5,8.1 Hz),8.11 (1H, s), 8.50 (1H, dd, J= 1.5, 5.1 Hz).
Elementary Analysis as $C_7H_7N_3 \cdot 0.25\ H_2O$
calc.: C,61.08 ; H,5.49 ; N,30.53
found: C,61.25 ; H,5.38 ; N,30.53 (%)

(compound 7)

[0073] ^{1}H-NMR ($CDCl_3$) δ : 3.94 (3H, s), 7.25 (1H, dd, J = 4.8, 8.1 Hz), 8.04 (1H, s), 8.08 (1H, dd, J = 1.5, 8.1 Hz), 8.43 (1H, dd, J = 1.5, 4.8 Hz).
Elementary Analysis as $C_7H_7N_3 \cdot 0.15\ H_2O$
calc.: C,61.89 ; H,5.42 ; N,30.93
found: C,61.72 ; H,5.54 ; N,30.79 (%)

Reference Example 3

[0074]



[0075] To a solution of compound 1 (Aldrich, 2.38 g, 20 mmol) in THF 100 ml, was added 60% NaH (880 mg, 1.1eq) under ice-cooling and the mixture was stirred at room temperature for 1.5 hr, then EtI (1.8 ml, 1.05eq) was added thereto under ice-cooling and the mixture was stirred at 4°C for 3 days. The reaction mixture was filtered and concentrated under reduced pressure, then water and AcOEt were added threto. The separated water layer was subjected to purification with HP-20 chromato. to give compound 10 (2.14 g, 72.7 %) and compound 11.

(compound 10)

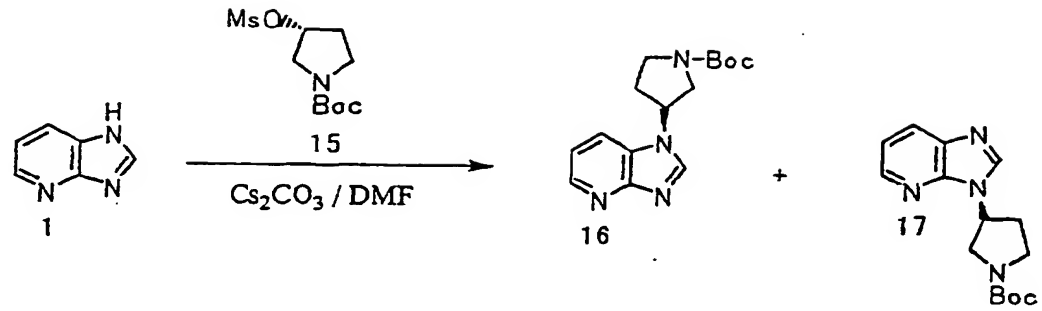
[0076] ^{1}H-NMR ($CDCl_3$) δ: 1.57 (3H, t, J = 7.5 Hz), 4.27 (2H, q, J = 7.5 Hz), 7.25 (1H, dd, J = 5.1, 8.1 Hz), 7.76 (1H, dd, J = 1.5, 8.1 Hz), 8.16 (1H, s), 8.58 (1H, dd, J = 1.5, 5.1 Hz).
IR (film) cm^{-1}: 3399, 3084, 3052, 2981, 1650, 1610, 1494, 1415, 1379, 1293, 1222, 783 .
Elementary Analysis as $C_8H_9N_3 \cdot 1.9\ H_2O$
calc.: C,52.97 ; H,7.11 ; N,23.16
found: C,53.12 ; H,7.16 ; N,23.18 (%)

(compound 11)

[0077] ^{1}H-NMR ($CDCl_3$) δ : 1.59 (3H, t, J = 7.5 Hz), 4.38 (2H, q, J = 7.5 Hz), 7.25 (1H, dd, J = 5.1, 8.1 Hz), 8.06 - 8.09 (2H, m), 8.16 (1H, s), 8.42 (1H, dd, J = 1.5, 5.1 Hz).

Reference Example 4

[0078]



[0079] To a solution of compound 1 (Aldrich, 3.3 g, 27.7 mmol) in DMF 28 ml, were added compound 15 (9 g, 1eq) and caesium carbonate (13.5 g, 1.5eq) and the mixture was stirred at 80°C for 2 hr. The reaction mixture was filtered and extracted with brine / AcOEt, then the organic layer was washed, dried over magnesium sulfate, and evaporated under reduced pressure. The residue was purified with silica gel chromatograph ($CHCl_3$ / MeOH = 9:1 - 4:1) to give compound 17 (2.47g, 30 %) in the nonpolor distillate and compound 16 (1.1g, 13.7 %) in the polor distillate.

(compound 16)

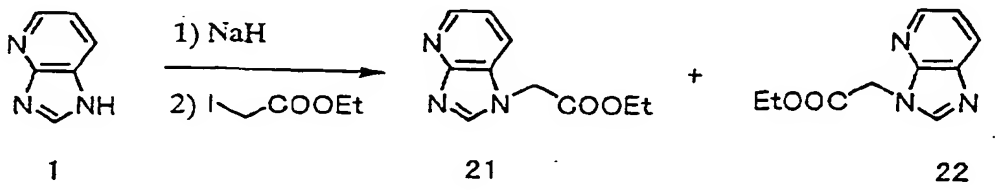
[0080] ^{1}H-NMR (d6-DMSO) δ : 1.39-1.43 (9H, m), 2.43 - 2.47 (2H, m), 3.52 - 3.60(2H, m), 3.83 - 3.89(1H, m), 5.20 (1H, brs), 7.30 (1H, dd, J = 4.8, 8.1 Hz) , 8.14 (1H, dd, J = 1.5, 8.1 Hz), 8.44(1H, dd, J = 1.5, 4.8 Hz) , 8.55 (1H, brs).
IR (Nujol) cm^{-1}; 3101, 1696, 1672, 1604, 1294, 1249, 1167, 1132, 788, 775.
Elementary Analysis as $C_{15}H_{20}N_4O_2$
calc.: C, 62.48 ; H,6.99 ; N,19.43
found: C,62.18 ; H, 6.90 ; N,19.32 (%)

(compound 17)

[0081] ^{1}H-NMR (d6-DMSO) δ: 1.41-1.44(9H, m), 2.5 (2H, brs), 3.31 - 3.88(4H, m), 5.26(1H, brs), 7.33 (1H, dd, J = 4.8, 8.1 Hz) , 8.12 (1H, dd, J = 1.5, 8.1 Hz), 8.40(1H, dd, J = 1.5, 3.6 Hz), 8.52(1H, brs).
IR (Nujole) cm^{-1}:3110, 1670, 1596, 1577, 1243, 1168, 1114, 773

Reference Example 5

[0082]



[0083] To a solution of compound 1 (5.11g,42.89mmol) in THF 220ml, was added 60%NaH (1.89 g, 1.1 eq) under ice-cooling in N_2 atomosphere and the mixture was stirred at room temperature for 15 min. The reaction mixture was cooled to -20°C and ethyl iodoacetic acetate (5.33 ml, 1.05 eq) was added thereto, then the mixture was stirred under ice-cooling for 1 hr. THF in the reaction mixture was evaporated under reduced pressure, to which AcOEt was added and the mixture was washed with saturated brine. The organic layer was isolated, dried over magnesium sulfate, concentrated under reduced pressure, and purified with silica gel chromatograph. AcOEt eluted compound 22 (2.31 g, yield: 26%), then 7% MeOH / AcOEt eluted compound 21 (4.67 g, 53%).

(compound 21)

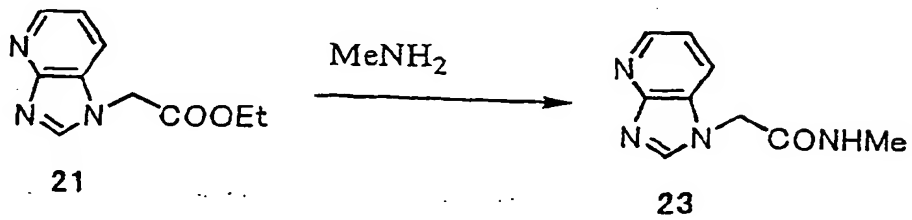
[0084] ^{1}H-NMR ($CDCl_3$) δ :1.29(3H, t, J=7.2 Hz), 4.27(2H, q, J=7. Hz), 5.10(2H, s), 7.28(1H, dd, J=8.0, 4.8 Hz),7.76 (1H, dd, J=8.0, 1.4 Hz),8.49(1H, dd, J=4.8, 1.4 Hz),8.51(1H s)
IR ($CHCl_3$) cm^{-1}:1755,1499,1420,1365,1295

(compound 22)

[0085] ^{1}H-NMR ($CDCl_3$) δ :1.29(3H, t, J=7.0 Hz), 4.27(2H ,q, J=7.0 Hz), 5.08(2H, s), 7.27(1H, dd, J=8.0, 4.8 Hz), 8.1(1H, dd, J=8.0, 1.4 Hz), 8.14(1H, s), 8.40(1H, dd, J=4.8, 1.4 Hz)
IR ($CHCl_3$) cm^{-1}:1749,1500,1415

Reference Example 6

[0086]

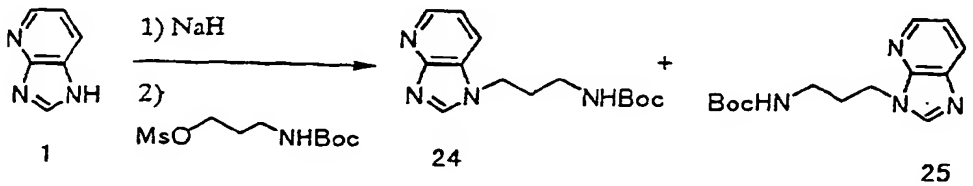


21 23

[0087] To a solution of compound21 (1.03g,5mmol) in MeOH 5ml, was added at room temperature a solution of 30% methylamine in MeOH 5ml and the mixture was stirred at the same temperature for 10 min. The reaction mixture was concentrated under reduced pressure to give compound 23 (0.95g, 100%, yellow crystal).
^{1}H-NMR($CDCl_3$)δ: 2.79(3H, d, J=4.5 Hz), 4.88(2H, s), 7.25(1H, dd, J=8.4,4.9 Hz), 7.75(1H, brs), 7.82(1H, dd, J=8.4, 1.4 Hz)
IR(Nujol)cm^{-1}:1670,1585

Reference Example 7

[0088]



1 24 25

[0089] To a solution of compound 1 (1.85g, 15.5 mmol) in DMF (15 ml), was added 60% NaH (0.68 g, 1.1eq.) in N_2 atmosphere under ice-cooling and the mixture was stirred at room temperature for 10 min. To the reaction mixture was added a solution of mesylate (4.34 g, 1.1eq.) in DMF (9 ml) and the mixture was stirred at 35°C for 20 hr. The reaction mixture was concentrated under reduced pressure, then the residue was purified with silica gel chromatograph to give compound 25 (2.54 g, 59%) from AcOEt elution and compound 24 (1.14 g, 27%) from 7% MeOH / AcOEt elution, respectively.

(compound 24)

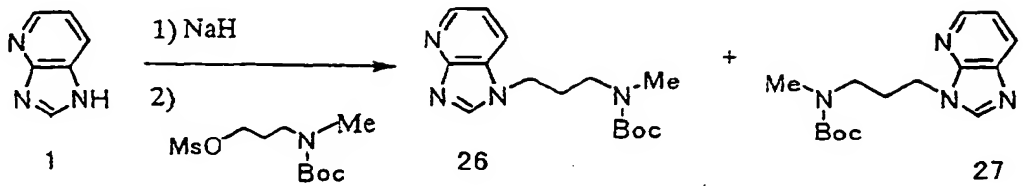
[0090] ^{1}H-NMR($CDCl_3$) δ :145(9H, s), 2.11(2H, m), 3.20(2H, m), 4.27(2H, t, J=10.5 Hz), 4.79(1H, brs), 7.25(1H, dd, J=11.7,7.2 Hz), 7,75(1H, dd, J=11.7,1.5 Hz), 8.21(1H, s),8.59(1H, dd, J=7.2,1.5 Hz)
IR($CHCl_3$)cm^{-1}:1700,1490,1160

(compound 25)

[0091] ^{1}H-NMR($CDCl_3$) δ : 1.46(9H, s), 2.10(2H, m), 3.12(2H, m), 4.40(2H, t, J=10.2 Hz), 5.30(1H, brs),7.27(1H, dd, J=9.9, 7.2 Hz), 8.10(1H, dd, J=9.9 Hz, 1.8 Hz), 8.12(1H, s),8.42(1H, dd, J=7.2, 1.8 Hz)
IR($CHCl_3$)cm^{-1}:1700,1495,1160

Reference Example 8

[0092]



[0093] To a solution of compound 1 (4.15 g, 34.84 mmol) in DMF (35 ml), was added 60% NaH (1.53 g, 1.1 eq.) under ice-cooling in N_2 atmosphere with stirring and the mixture was further stirred at room temperature for 15 min. To the reaction mixture was added a solution of mesylate (10.26 g, 1.1 eq.) in DMF 20ml and the mixture was stirred at 50°C for 1.5 hr. The reaction mixture was concentrated under reduced pressure, then the residue was purified with silica gel chromatograph to give compound 27 (5.94 g, 59%) from AcOEt elution and compound 26 (2.90 g, 29%) from 6% MeOH/AcOEt elution.

(compound 26)

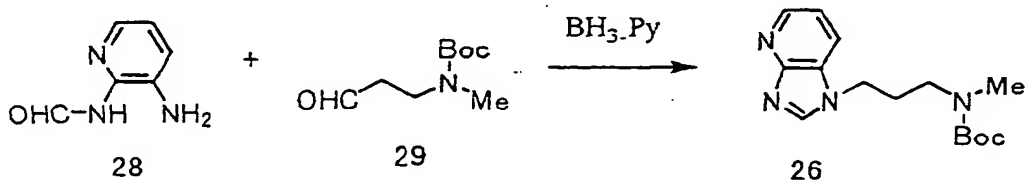
[0094] ^{1}H-NMR($CDCl_3$) δ : 1.45(9H, s), 2.12(2H, m), 2.85(3H, s), 3.32(2H, t, J=6.8 Hz), 4.22(2H, t, J=7.0 Hz),7.25 (1H, dd, J=8.2, 4.8 Hz),7.74(1H, dd. J=8.2, 1.4 Hz),8.20(1H, s),8.60(1H, dd, J=4.8, 1.4 Hz)
IR($CHCl_3$)cm^{-1};1670,1480,1465,1400,1380,1350

(compound 27)

[0095] ^{1}H-NMR($CDCl_3$) δ :1.44(9H, s), 2.18(2H, m), 2.85(3H, s), 3.30(2H, t, J=6.8 Hz), 4.32(2H, t, J=7.2 Hz),7.25 (1H, dd, J=8.1, 4.8 Hz),8.08(1H, dd, J=8.1, 1.4 Hz),8.15(1H, s),8.40(1H, dd, J=4.8, 1.4 Hz)
IR($CHCl_3$)cm^{-1}:1681,1500,1410,1395,1369

Reference Example 9

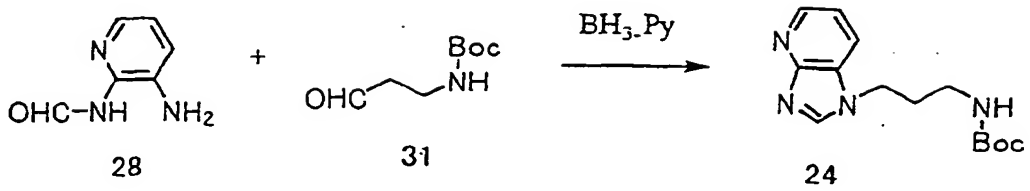
[0096]



[0097] To a suspension of compound 28 (5.76 g, 42 mmol) and compound 29 (8.22 g, 1 eq.) in methylene chloride 40ml, was added an ice-cooled mixture of methylene chloride 20ml and AcOH 60ml at - 10°C under stirring, to which was added a borane-pyridine complex (4.44 ml, 1 eq.) and the mixture was stirred at room temperature for 1 hr. The organic layer was separated, washed with a saturated brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified with silica gel chromatograph with 10% MeOH / AcOEt to give compound 26 (11.25 g, 92%). The physical data was identical to that of Reference Example 8.

Reference Example 10

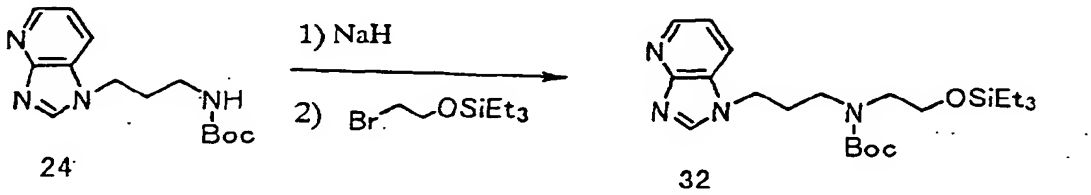
[0098]



[0099] To a suspension of compound 28 (8.8 g, 64.16 mmol) and compound 31 (12.5 g, 1.1 eq.) in CH_2Cl_2 120ml, was added AcOH 91ml and a borane-pyridine complex successively under ice-cooling and the mixture was stirred at room temperature for 1 hr. The reaction mixture was added to an ice-cooled solution (91 ml) of 28% ammonia water and AcOEt under stirring. The organic layer was separated, washed with a saturated brine, dried over $MgSO_4$, and concentrated under reduced pressure. The obtained residue was purified with silica gel chromatograph with 10% MeOH / AcOEt to give compound 24 (14.28 g, 80.5%). The physical data was identical to that of Reference Example 7.

Reference Example 11

[0100]

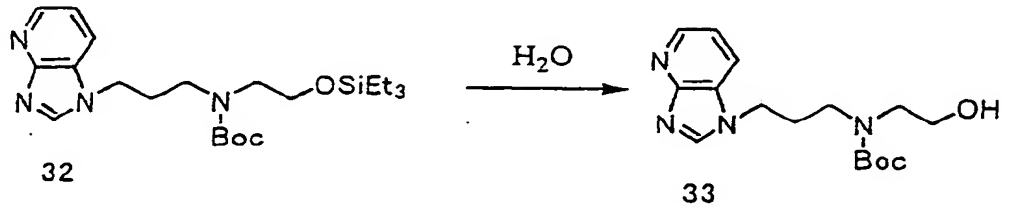


[0101] To a solution of compound 24 (1.14 g, 4.13 mmol) in DMF (6 ml), was added in N_2 atmosphere 60% NaH (0.25 g, 1.5eq.) and the mixture was stirred at room temperature for 10 min. To the reaction mixture was added a solution of bromine compound (1.48 g, 1.5 eq.) in DMF (2ml), and the mixture was stirred at room temperature for 1 hr, then 60% NaH (0.17 g, 1 eq.) and the same bromine compound (0.99 g, 1eq.) were added thereto at room temperature under stirring for 2 hr. The reaction mixture was poured into a mixture of ice water and AcOEt under stirring. The organic layer was separated, washed with water and a saturated brine successively, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified with silica gel chromatograph (5% MeOH / AcOEt) to give compound 32 (1.26 g, 70%).

^{1}H-NMR($CDCl_3$) δ: 0.57(9H, q, J=7.8 Hz), 0.93(6H, t, J=7.8 Hz), 1.46(9H, s), 2.15(2H, m), 3.25(2H, brs), 3.38(2H, brs), 3.68 (2H, m), 4.21(2H, t, J=7.2 Hz), 7.25(1H, dd, J=7.8, 4.5 Hz), 7.75(1H, dd, J=7.8, 1.2 Hz), 8.30(1H, s), 8.59(1H, dd, J=4.5, 1.2 Hz)

Reference Example 12

[0102]



[0103] Compound 32 (1.26 g, 2.9 mmol) was mixed with THF 6ml, AcOH 3ml, and water 6 ml, and the mixture was

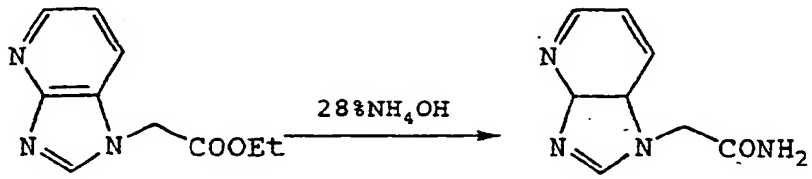
stirred at room temperature for 30 min. The reaction mixture was poured into ice water / AcOEt with stirring. The water layer was separated, then which was adjusted to pH 8 with Na_2CO_3 for salting-out, and extracted with AcOEt. The organic layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure to give compound 33 (0.93 g, 100%).

^{1}H-NMR($CDCl_3$) δ : 1.42(9H, s), 2.18(2H, m), 3.38(4H, m), 3.78(2H, t, J=5.1 Hz), 4.23(2H, t, J=7.5 Hz),7.21(1H, dd, J=8.1, 3.9 Hz), 7.74(1H, dd, J=8.1, 1.2 Hz),8.17(1H, s),8.55(1H, dd, J=3.9 Hz, 1.2 Hz)

IR(Nujol)cm^{-1}:3160,1690,1420,1050

Reference Example 13

[0104]



21 43

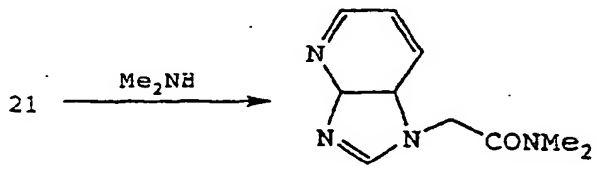
[0105] To a solution of compound 21 (3.47 g, 16.7 mmol) of Reference Example 5 in EtOH 20ml, was added 28% ammonia water 20ml at room temperature under stirring and the mixture was further stirred for 30 min. The reaction mixture was concentrated under reduced pressure and the residue was purified with HP-20SS to give compound 43 (1.41 g, yield 48%).

^{1}H-NMR(DMSO-d6) δ :4.96(2H,S), 7.27(1H,dd,J=8.2Hz,4.8Hz), 7.37(1H,S), 7.76(1H,S), 7.92(1H,dd,J=8.2Hz,1.6Hz), 8.40(1H,dd,J=4.8Hz,1.6Hz), 8.41(1H,S)

IR(Nujol)cm^{-1}:3340,1665,1420,1395,1299

Reference Example 14

[0106]



44

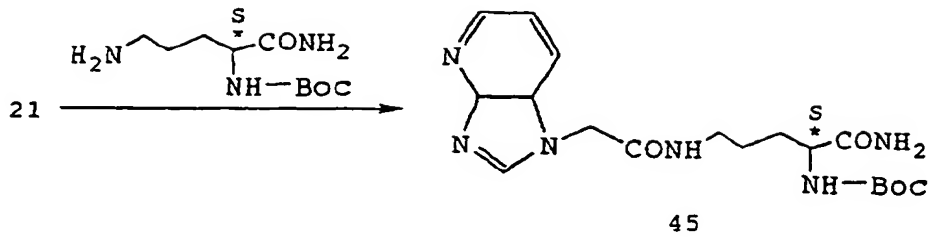
[0107] To a solution of compound 21 (1.03 g, 5 mmol) of Reference Example 13 in MeOH 5ml, was added 50% dimethylamine aqueous solution 5ml at room temperature with stirring for 30 min. The reaction mixture was concentrated under reduced pressure and the crystalline residue was washed with i-PrOH to give compound 44 (0.75 g, 73%).

^{1}H-NMR(DMSO-d6) δ :2.87(3H,S), 3.12(3H,S), 5.32(2H,S), 7.25(1H,dd,J=8.0Hz,4.8Hz), 7.95(1H,dd,J=8.0Hz,1.0Hz), 8.34(1H,S), 8.40(1H,dd,J=4.8Hz,1.0Hz)

IR(Nujol)cm^{-1}:1639,1480,1403,1280

Reference Example 15

[0108]



45

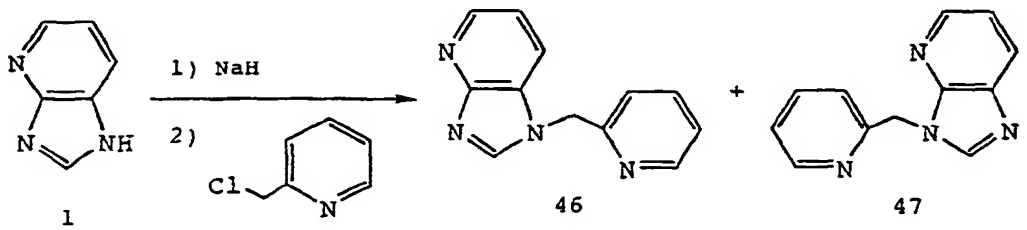
[0109] To a solution of compound 21 (1.01 g) of Reference Example 13 in MeOH 5ml, was added a solution of amino compound (1.14 g, 1 eq.) in MeOH 5ml under stirring at room temperature and the mixture was stirred for 4 hr. The reaction mixture was concentrated under reduced pressure and the residue was purified with HP-20 to give compound 45 (1.40 g, yield 73%).

^{1}H-NMR(CD_3OD) δ :1.44(9H,S), 1.6 ~ 2.0(4H,m), 3.3(2H,m), 4.0(1H,m), 5.06(2H,S), 7.38(1H,dd,J=8.2Hz,5.0Hz), 8.0 (1H,dd,J=8.2Hz, 1.4Hz), 8.42(1H,S), 8.46(1H,dd,J=5.0Hz,1.4Hz)

IR(Nujol)cm^{-1}:3300,1670,1460,1365

Reference Example 16

[0110]



1 46 47

[0111] To a solution of compound 1 (2.38 g, 20 mmol) in DMF 15ml, was added NaH (60% suspension in mineral oil, 0.88 g, 1.1 eq.) under ice-cooling in N_2 atmosphere and the mixture was stirred at room temperature for 10 min. To another solution containing 2-picolyl chloride hydrochloride (3.61 g, 1.1 eq.) in DMF 15ml, was added NaH (60% suspension in mineral oil, 0.88 g, 1.1 eq.) under ice-cooling in N_2 atmosphere and the mixture was stirred at the same temperature for 15 min. Thus obtained both reaction mixtures were put together under ice-cooling to stir at room temperature for 1 hr. The final reaction mixture was concentrated under reduced pressure and the residue was purified with silica gel chromatograph to give compound 47 (2.05 g, yield 49%) from AcOEt elution and compound 46 (1.24 g, yield 30%) from 7% MeOH / AcOEt elution.

(compound 46)

[0112] ^{1}H-NMR($CDCl_3$) δ :5.50(2H,S), 7.0(1H,d,J=8.1Hz), 7.24(2H,m), 7.66(2H,m), 8.29(1H,S), 8.59(2H,m)

IR($CHCl_3$)cm^{-1}:1610,1590,1490,1415,1290

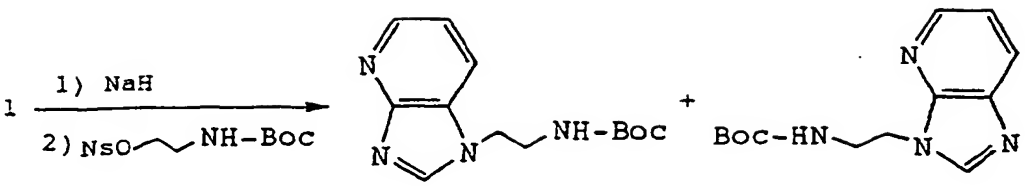
(compound 47)

[0113] ^{1}H-NMR($CDCl_3$) δ :5.61(2H,S), 7.24(2H,m), 7.63(1H,m), 8.09(1H,m), 8.25(1H,S), 8.42(1H,m), 8.59(1H,m)

IR($CHCl_3$)cm^{-1}:1599,1500,1410,1281

Reference Example 17

[0114]



48 49

[0115] To a solution of compound 1 (1.19 g, 10 mmol) of Reference Example 16 in THF 50ml, was added NaH (60% suspension in mineral oil, 0.44 g, 1.1 eq.) under stirring in N_2 atmosphere under ice-cooling and the mixture was stirred at room temperature for 15 min. To the reaction mixture was added a solution of mesylate (2.52 g, 1.1eq.) in THF (10 ml) and the mixture was stirred at room temperature for 3 days. The reaction mixture was concentrated under reduced pressure and the residue was purified with silica gel chromatograph to give compound 48 (0.95 g, yield 36%) from 5% MeOH / AcOEt elution and compound 49 (0.48 g, yield 18%) from 8% MeOH / AcOEt elution.

(compound 48)

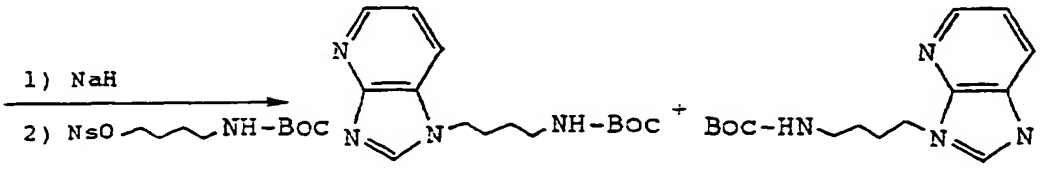
[0116] ^{1}H-NMR($CDCl_3$) δ :1.45(9H,S), 3.57(2H,q,J=6.0Hz), 4.36(2H,t,J=6.0Hz), 5.51(1H,S), 7.17(1H,dd,J=8.2Hz, 4.8Hz), 7.75(1H,dd,J=8.2Hz,1.6Hz), 8.01(1H,S), 8.47(1H,dd,J=4.8Hz,1.6Hz)
IR($CHCl_3$)cm^{-1}:3450,1703,1499,1409,1370

(compound 49)

[0117] ^{1}H-NMR($CDCl_3$) δ :1.40(9H,S), 3.60(2H,q,J=5.8Hz), 4.46(2H,t,J=5.8Hz), 5.00(1H,S), 7.25(1H,dd,J=8.0Hz, 4.8Hz), 8.03(1H,S), 8.07(1H,dd,J=8.0Hz,1.6Hz), 8.39(1H,dd,J=4.8Hz,1.6Hz)
IR($CHCl_3$)cm^{-1}:3450,1705,1500,1410,1365

Reference Example 18

[0118]



50 51

[0119] To a solution of compound 1 (1.87 g, 15.7 mmol) of Reference Example 16 in DMF 15ml, was added NaH (60% suspension in mineral oil, 0.69 g, 1.1eq.) under stirring in N_2 atmosphere under ice-cooling and the mixture was stirred at room temperature for 10 min. To the reaction mixture was added a solution of mesylate (4.62 g, 1.1 eq.) in DMF (8ml) and the mixture was stirred at room temperature for 16 hr. The reaction mixture was concentrated under reduced pressure and the residue was purified with silica gel chromatograph to give compound 51 (2.77 g, yield 61%) from AcOEt elution and compound 50 (0.98 g, yield 22%) from 7% MeOH / AcOEt elution.

(compound 50)

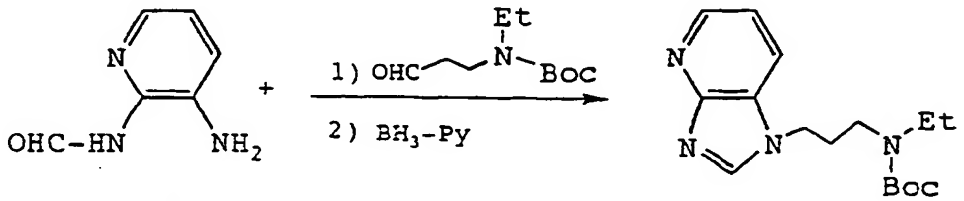
[0120] ^{1}H-NMR($CDCl_3$) δ :1.44(9H,S), 1.52(2H,m), 1.93(2H,m), 3.18(2H,m), 4.25(2H,t,J=6.9Hz), 4.65(1H,S), 7.23 (1H,dd,J=8.1Hz,4.8Hz), 7.77(1H,dd,J=8.1Hz,1.2Hz), 8.12(1H,S), 8.58(1H,dd,J=4.8Hz,1.2Hz)
IR($CHCl_3$)cm^{-1}:3460,1705.1505,1495

(compound 51)

[0121] ^{1}H-NMR($CDCl_3$) δ :1.44(9H,S), 1.55(2H,m), 1.98(2H,m), 3.18(2H,m), 4.34(2H,t,J=7.2Hz), 4.70(1H,S), 7.25 (1H,m), 8.07(1H,S), 8.07(1H,m), 8.40(1H,d,J=4.8Hz)
IR($CHCl_3$)cm^{-1}:3460,1705,1500

Reference Example 19

[0122]

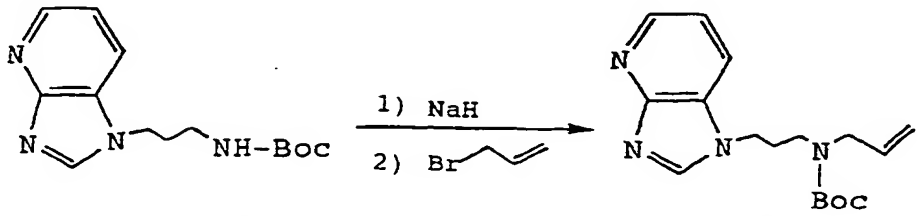


52 53

[0123] To a suspension of compound 52 (0.97 g, 7.1 mmol) and aldehyde (1.43 g, 1 eq.) in CH_2Cl_2 6ml, was added an ice-cooled solution of CH_2Cl_2 4ml-AcOH10ml under stirring and a borane-pyridine complex (0.72ml, 1eq.) successively, then the mixture was stirred room temperature for 1 hr. The reaction mixture was added to an ice-cooled solution of 28% ammonia water (10ml) and AcOEt with stirring. The organic layer was separated, washed with a saturated brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified with silica gel chromatograph to give compound 53 (1.75 g, yield 81%) from 10% MeOH / AcOEt elution.
^{1}H-NMR($CDCl_3$) δ : 1.08(3H,t,J=6.9Hz), 1.44(9H,S), 2.12(2H,m), 3.25(4H,m), 4.22(2H,t,J=7.5Hz), 7.20(1H,dd, J=8.4Hz,4.5Hz), 7.74(1H,dd,J=8.4Hz,1.5Hz), 8.20(1H,S), 8.59(1H,dd,J=4.5Hz,1.5Hz)
IR($CHCl_3$)cm^{-1}:1680,1479,1415,1285

Reference Example 20

[0124]



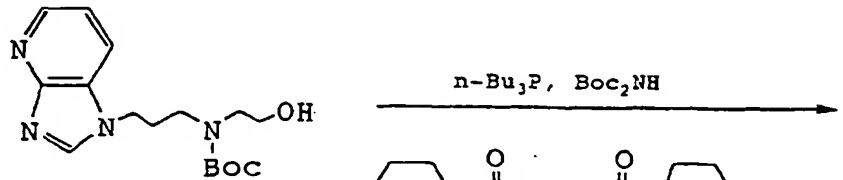
24 54

[0125] To a solution of compound 24 (0.63 g, 2.28 mmol) of Reference Example 10 in DMF 3ml, was added NaOH (0.11 g, 1.2 eq.) under stirring at room temperature in N_2 atmosphere and the mixture was stirred at room temperature for 10 min. To the reaction mixture was added allyl bromide (237μl, 1.2 eq.) under ice-cooling and the mixture was stirred at room temperature for 1 hr. The reaction mixture was poured into ice water / AcOEt, then the organic layer was separated, washed with a saturated brine, dried over $MgSO_4$, concentrated under reduced pressure. The residue was purified with silica gel chromatograph to give compound 54 (0.41 g, yield 57%) from 10% MeOH / AcOEt elution.
^{1}H-NMR($CDCl_3$) δ :1.44(9H,S), 2.11(2H,m), 3.28(2H,m), 3.78(2H,m), 4.21(2H,t,J=7.2Hz), 5.09(2H,m), 5.74(1H,m),

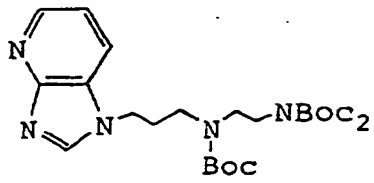
7.20(1H,dd,J=8.1Hz,4.5Hz), 7.73(1H,dd,J=8.1Hz,1.5Hz), 8.18(1H,S), 8.59(1H,dd,J=4.6Hz,1.5Hz)
IR($CHCl_3$)cm^{-1}:1675,1480,1410,1350

Reference Example 21

[0126]



33

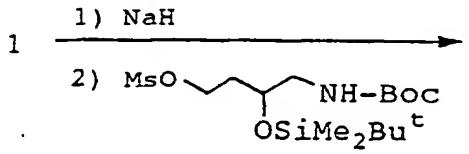


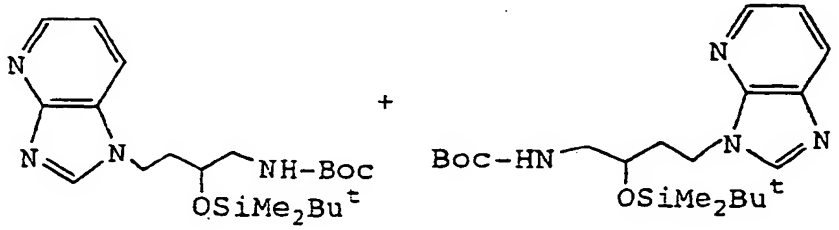
55

[0127] To a solution of compound 33 (0.97 g, 3.02 mmol) of Reference Example 12 in THF 15 ml, were added tri-n-butylphosine (1.13 ml, 1.5 eq.), di-tert-butyliminodicarboxylate (0.995 g, 1.5 eq.), and 1,1'-azodicarbonyldipiperidine (1.15 g, 1.5 eq.) under ice-cooling with stirring 15 min, then the mixture was further stirred room temperature for 3 hr. To the reaction mixture were added the above 3 kinds of reagents each 0.5 eq. and the mixture was stirred at room temperature for 2 hr. The reaction mixture was filtered to remove insoluble products, then the filtlate was dissolved in AcOEt, which was washed, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified with silica gel chromatograph to give compound 55 (1.14 g, yield 72%) from 2% MeOH / $CHCl_3$ elution.
^{1}H-NMR($CDCl_3$) δ :1.48(27H,S), 2.13(2H,m), 3.37(4H,m), 3.73(2H,d,J=6.2Hz), 4.21(2H,d,J=7.4Hz), 7.91(1H,dd, J=7.8Hz,4.8Hz), 7.75(1H,dd,J=7.8Hz,1.2Hz), 8.24(1H,S), 8.58(1H,dd,J=4.8Hz,1.2Hz)
IR($CHCl_3$)cm^{-1}:1680,1478,1420,1290

Reference Example 22

[0128]





56 57

[0129] Compound 1 (1.03 g, 8.61 mmol) of Reference Example 16 was dissolved in DMF 8ml, which was treated with 1.1 eq. of NaH and the mesylate according to Reference Example 18, to give compound 56 (0.89 g, yield 25%) and compound 57 (1.43 g, yield 39%).

(compound 56)

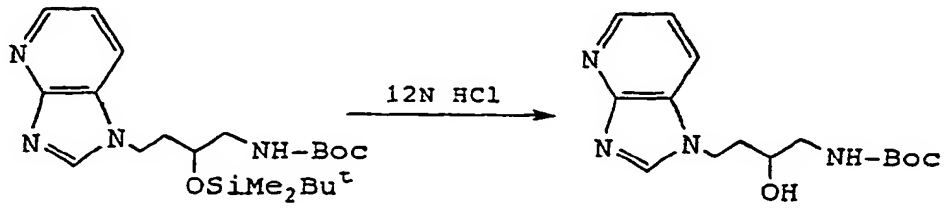
[0130] ^{1}H-NMR($CDCl_3$) δ :0.07(3H,S), 0.08(3H,S), 0.92(9H,S), 1.45(9H,S), 2.04(2H,m), 3.21(2H,m), 3.86(1H,m), 4.31(2H,m), 4.78(1H,m), 7.23(1H,dd,J=8.4Hz,4.8Hz), 7.78(1H,dd,J=8.4Hz,1.5Hz), 8.14(1H,S), 8.58(1H,dd,J=4.8Hz, 1.5Hz)
IR($CHCl_3$)cm^{-1}:3460,1704,1500,1365

(compound 57)

[0131] ^{1}H-NMR($CDCl_3$) δ :0.05(3H,S), 0.06(3H,S), 0.91(9H,S), 1.44(9H,S), 2.12(2H,m), 3.24(2H,m), 3.89(1H,m), 4.38(2H,t,J=7.2Hz), 4.94(1H,m), 7.20(1H,dd,J=8.1Hz,4.8Hz), 8.07(1H,dd,J=8.1Hz,1.2Hz), 8.08(1H,S), 8.40(1H,dd, J=4.8Hz,1.2Hz)
IR($CHCl_3$)cm^{-1}:3460,1702,1510,1360

Reference Example 23

[0132]

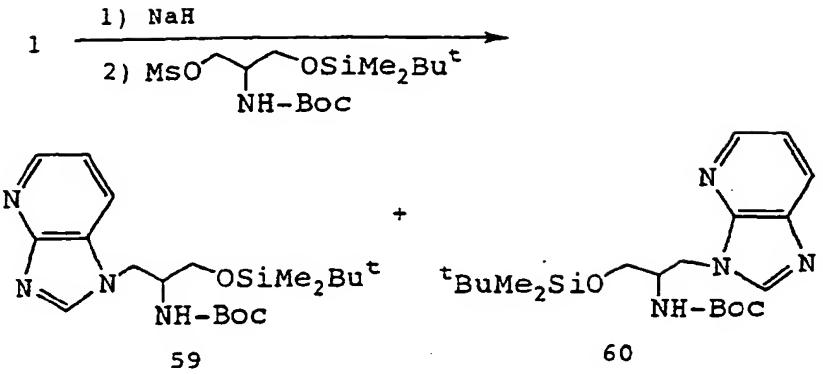


56 58

[0133] To a solution of compound 56 (0.89 g, 2.12 mmol) in MeCN 6ml, was added 12N HCl (0.35 ml, 2 eq.) and the mixture was stirred at room temperature for 30 min. To the reaction mixture was added water and AcOEt with stirring, then the water layer was separated and basified with Na_2CO_3. The obtained solution was concentrated under reduced pressure up to 3ml, then a solution of $(Boc)_2O$ 490 μ ml in dioxane 4ml was added thereto at 50°C and the mixture was stirred for 1 hr. The reaction mixture was concentrated under reduced pressure and the residue was purified with silica gel chromatograph to give compound 58 (0.36 g, yield 56%).
^{1}H-NMR($CDCl_3$) δ :1.40(9H,S), 2.00(2H,m), 3.21(2H,m), 3.50(1H,m), 4.48(2H,m), 6.0(1H,m), 7.22(1H,dd,J=8.0Hz, 5.0Hz), 7.82(1H,dd,J=8.0Hz,1.6Hz), 8.23(1H,S) 8.53(1H,dd,J=5.0Hz,1.6Hz)
IR($CHCl_3$)cm^{-1}:3450,1695,1500,1495

Reference Example 24

[0134]



59 60

[0135] Compound 1 (1.93 g, 16.2 mmol) of Reference Example 16 was dissolved in DMF 15 ml, which was treated with 1.1 eq. of NaH and the mesylate according to Reference Example 18, to give compound 59 (0.57 g, yield 9%) and compound 60 (3.85 g, yield 58%).

(compound 59)

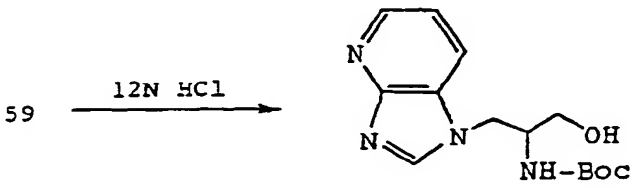
[0136] ^{1}H-NMR($CDCl_3$) δ :0.10(6H,S), 0.96(9H,S), 1.45(9H,S), 3.53(2H,m), 4.05(1H,m), 4.37(2H,d,J=6.6Hz), 4.88 (1H,d,J=8.2Hz), 7.24(1H,dd,J=8.2Hz,4.6Hz), 7.96(1H,dd,J=8.2Hz,1.6Hz), 8.08(1H,S), 8.57(1H,dd,J=4.6Hz,1.6Hz)
IR($CHCl_3$)cm^{-1}:3440,1705,1498,1410,1365

(compound 60)

[0137] ^{1}H-NMR($CDCl_3$) δ :0.07(6H,S), 0.93(9H,S), 1.37(9H,S), 3.51(1H,m), 3.69(1H,m), 4.14(1H,m), 4.48(2H,d, J=5.4Hz), 5.51(1H,m), 7.24(1H,dd,J=8.4Hz,4.8Hz), 8.06(1H,S), 8.08(1H,dd,J=8.4Hz,1.5Hz), 8.40(1H,dd,J=4.8Hz, 1.5Hz)
IR($CHCl_3$)cm^{-1}:3450,1708,1495,1410,1363

Reference Example 25

[0138]

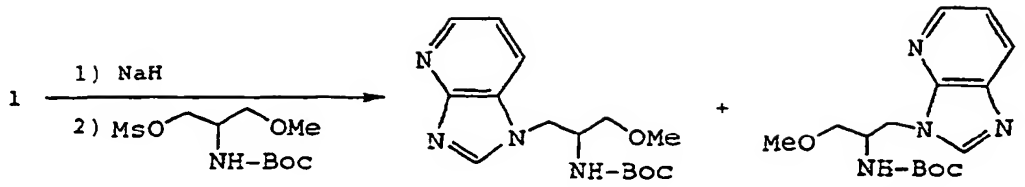


61

[0139] Compound 59 (0.57 g, 1.4 mmol) of Reference Example 24 was dissolved in MeCN 4ml, then which was treated with 12N HCl 0.23ml according to Reference Example 23, to give compound 61 (0.40 g, 97%).
^{1}H-NMR($CDCl_3$) δ :1.43(9H,S), 3.70(2H,m), 4.06(1H,m), 4.50(2H,m), 6.07(1H,d,J=7.2Hz), 7.25(1H,dd,J=8.4Hz, 5.1Hz), 8.07(1H,dd,J=8.4Hz,2.1Hz), 8.20(1H,S), 8.50(1H,dd,J=5.1Hz,2.1Hz)
IR($CHCl_3$)cm^{-1}:3430,1695,1490,1413,1361,1285

Reference Example 26

[0140]



62 63

[0141] Compound 1 (1.06 g. 8.9 mmol) of Reference Example 16 was dissolved in DMF 8ml, then which was treated with 1.1 eq. of NaH and the mesylate according to Reference Example 18, to give compound 62 (0.36 g, yield 19%) and compound 63 (1.43 g, 52%).

(compound 62)

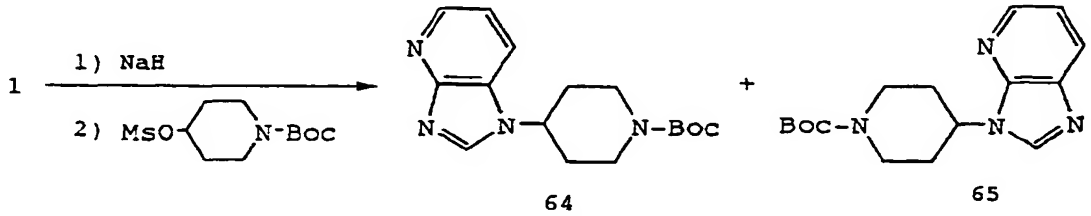
[0142] ^{1}H-NMR($CDCl_3$) δ :1.45(9H,S), 3.28(2H,m), 3.37(3H,S), 4.11(1H,m), 4.37(2H,d,J=6.6Hz), 5.10(1H,m), 7.29 (1H,dd,J=7.8Hz,4.2Hz), 7.95(1H,dd,J=7.8Hz,1.6Hz), 8.13(1H,S), 8.60(1H,dd,J=4.2Hz,1.6Hz)
IR($CHCl_3$)cm^{-1}:3440,1705,1500,1410,1365

(compound 63)

[0143] ^{1}H-NMR($CDCl_3$) δ :1.36(9H,S), 3.34(3H,S), 3.38(2H,m), 4.22(1H,m), 4.49(2H,d,J=5.6Hz), 5.55(1H,m), 7,25 (1H,dd,J=8.0Hz,5.0Hz), 8.05(1H,S), 8.08(1H)dd,J=8.0Hz,1.4Hz), 8.40(1H,dd,J=5.0Hz,1.4Hz)
IR($CHCl_3$)cm^{-1}:3440,1708,1500,1408,1370

Reference Example 27

[0144]



64 65

[0145] Compound 1 (2.14 g, 17.96 mmol) of Reference Example 16 was dissolved in DMF 15ml, then which was treated with 1.1 eq. of NaH and the mesylate according to Reference Example 18, to give compound 64 (1.11 g, yield 20%) and compound 65 (1.86 g, yield 34%).

(compound 64)

[0146] ^{1}H-NMR($CDCl_3$) δ :1.51(9H,S), 2.14(4H,m), 2.94(1H,m), 4.37(4H,m), 7.25(1H,dd,J=8.2Hz,4.6Hz), 7.79(1H, dd,J=8.2Hz,1.4Hz), 8.21(1H,S), 8.60(1H,dd,J=4.6Hz,1.4Hz)
IR($CHCl_3$)cm^{-1}:1681,1480,1450,1415,1362

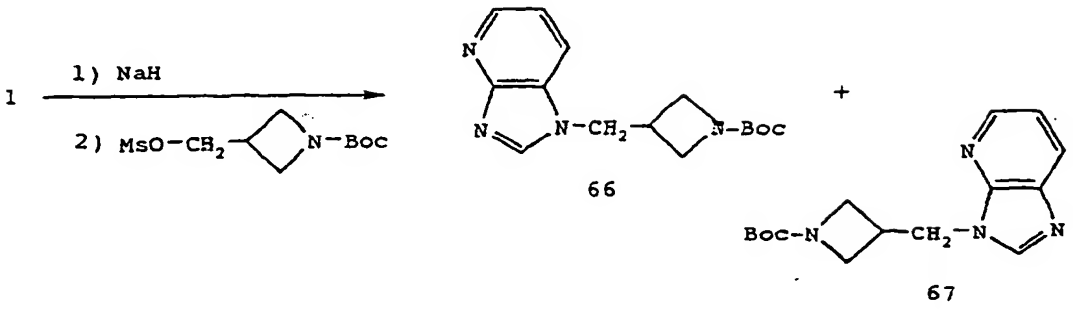
(compound 65)

[0147] ^{1}H-NMR($CDCl_3$) δ :1.50(9H,S), 2.10(4H,m), 2.94(1H,m), 4.35(4H,m), 7.26(1H,dd,J=8.0Hz,4.6Hz), 8.09(1H,

dd,J=8.0Hz,1.2Hz), 8.12(1H,S), 8.40(1H,dd,J=4.6Hz,1.2Hz)
IR($CHCl_3$)cm^{-1}:1681,1488,1421,1405,1363

Reference Example 28

[0148]



[0149] Compound 1 (0.78 g, 6.57 mmol) of Reference Example 16 in DMF 6ml, then which was treated with 1.1 eq. of NaH and the mesylate according to Reference Example 18, to give compound 66 (0.42 g, yield 22%) and compound 67 (1.09 g, yield 57%).

(compound 66)

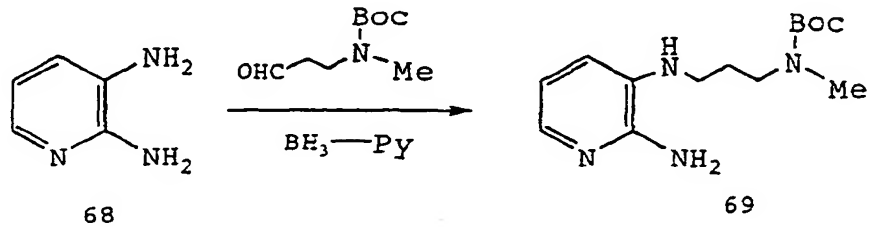
[0150] ^{1}H-NMR($CDCl_3$) δ:1.44(9H,S), 3.08(1H,m), 3.70(2H,m), 4.06(2H,m), 4.43(2H,d,J=7.8Hz), 7.27(1H,dd, J=7.8Hz,4.6Hz), 7.76(1H,dd,J=7.8Hz,1.6Hz), 8.14(1H,S), 8.61(1H,dd,J=4.6Hz,1.6Hz)
IR($CHCl_3$)cm^{-1}:1685,1503,1415,1370

(compound 67)

[0151] ^{1}H-NMR($CDCl_3$) δ:1.44(9H,S), 3.20(1H,m), 3.77(2H,m), 4.04(2H,m), 4.52(2H,d,J=7.8Hz), 7.27(1H,dd, J=8.2Hz,4.8Hz), 8.07(1H,S), 8.09(1H,dd,J=8.2Hz,1.6Hz), 8.41(1H,dd,J=4.8Hz,1.6Hz)
IR($CHCl_3$)cm^{-1}:1688,1500,1416,1370

Reference Example 29

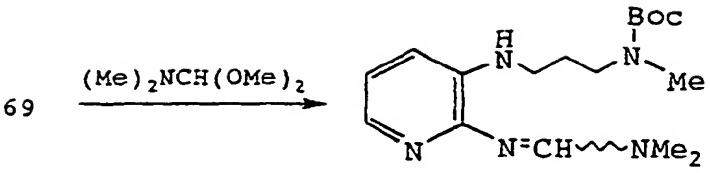
[0152]



[0153] Compound 68 (161.5 g, 1.48 mol) was added to a mixture of CH_2Cl_2 1.6 ml and AcOH 1.6 ml and the resulting mixture was stirred at room temperature, then cooled to -15°C. A borane / pyridine complex (150 ml, 1 eq.) and a solution of aldehyde (360.2 g, 1.3 eq.) in CH_2Cl_2 300ml were added thereto successively, and the mixture was stirred at -15°C for 1 hr. The reaction mixture was washed with NaOH aq. and a saturated brine successively, then the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give compound 69 (289 g, yield 69.6%).
mp.101~4°C (AcOH / Et_2O)
^{1}H-NMR($CDCl_3$) δ:1.44(9H,S), 1.82(2H,m), 2.84(3H,S), 3.09(2H,t,J=6.6Hz), 3.56(2H,t,J=6.6Hz), 6.66(1H,m), 6.75 (1H,m), 7.55(1H,d,J=4.3Hz)
IR($CHCl_3$)cm^{-1}: 1680,1485,1460,1405

Reference Example 30

[0154]

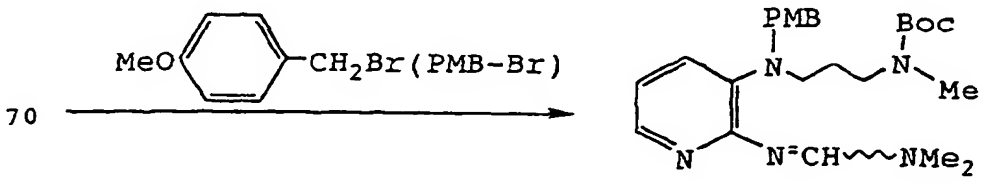


70

[0155] Compound 69 (200 g, 0.713 mol) of Reference Example 29 was dissolved in N,N-dimethylformamideacetal (142 ml, 1.5 eq.) and the mixture was stirred at 70°C for 4 hr. The reaction mixture was poured into a mixture of AcOEt and water for extraction. The AcOEt layer was separated, washed with a saturated brine, dried over Na_2SO_4, and evaporated under reduced pressure to give compound 70 (239 g, yield 100%).
^{1}H-NMR($CDCl_3$) δ :1.45(9H,S), 1.87(2H,m), 2.87(3H,S), 3.09(6H,S), 3.13(2H,t,J=6.4Hz), 3,34(2H,t,J=6.9Hz), 6.74(2H, m) 7.56(1H,dd,J=4.8Hz,1.6Hz), 8.44(1H,S)
IR($CHCl_3$)cm^{-1}:1685,1635,1590,1580,1485,1395

Reference Example 31

[0156]

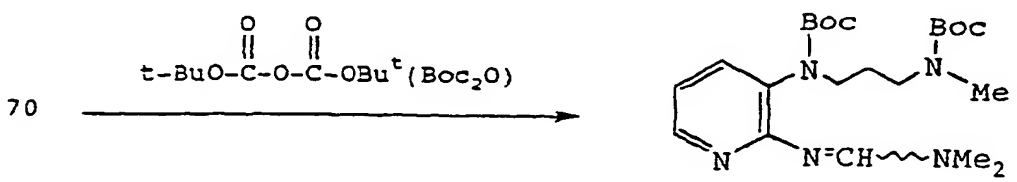


71

[0157] To a solution of compound 70 (50.8 g, 0.151 mol) of Reference Example 30 in DMF 250ml, were added $NaHCO_3$ 38.17 g and p-methoxybenzyl bromide (PMB-Br, 33.5 g, 1.1 eq.) under stirring and the mixture was stirred at 25°C for 3.5 hr. The reaction mixture was dissolved in AcOEt, which was washed with a saturated saline, dried over Na_2SO_4, and evaporated under reduced pressure to give compound 71 (59.46 g, yield 86%).
^{1}H-NMR($CDCl_3$) δ :1.39(9H,S), 1.65(2H,m), 2.70(3H,S), 3.03(3H,S), 3.07(3H,S), 3.10(4H,m), 3.78(3H,S), 4.37(2H,S), 6.80(3H,m), 7.03(1H,dd,J=7.9Hz,1.7Hz), 7.23(2H,d,J=8.7Hz), 7.87(1H,dd,J=4.7Hz,1.6Hz), 8.33(1H,S)
IR($CHCl_3$)cm^{-1}:1685,1635,1580,1520,1405

Reference Example 32

[0158]

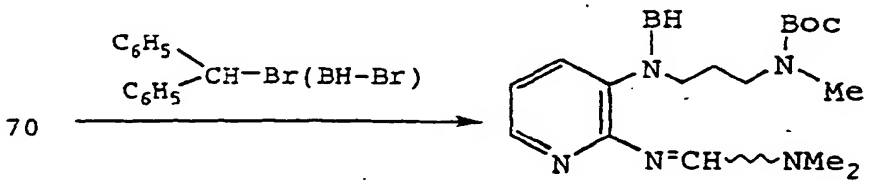


72

[0159] Compound 70 (312 g, 0.9291 mol) of Reference Example 30 and di-t-butyldicarbonate (243 g, 1.2 eq.) were dissolved in THF 624 ml and the mixture was refluxed under stirring for 3.5 hr. The reaction mixture was evaporated under reduced pressure to remove THF, then AcOEt was added to the residue, followed by etraction with a 10% aqueous solution of oxalic acid. The water layer was separated and basified with 4N NaOH aq., then which was extracted with AcOEt, washed, dried over Na_2SO_4, and evaporated to give compound 72 (356.9 g, yield 85%).
^{1}H-NMR(DMSO-d6) δ :1.21(9H,S), 1.35(9H,S), 1.59(2H,m), 2.70(3H,S), 2.96(3H,S), 3.08(3H,S), 3.15(2H,t,J=7.1Hz), 6.89(1H,dd,J=7.6Hz,4.8Hz), 7.42(1H,dd,J=7.6Hz,1.6Hz), 8.08(1H,dd,J=4.8Hz,1.6Hz), 8.44(1H,S)
IR($CHCl_3$)cm^{-1}:1690,1638,1585,1465,1405

Reference Example 33

[0160]

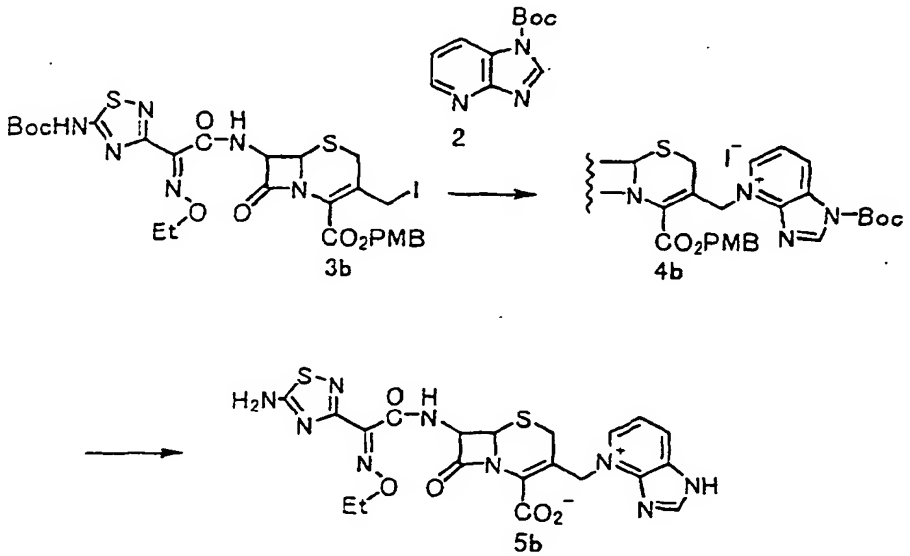


73

[0161] To a solution of compound 70 (3.50 g, 10 mmol) of Reference Example 30 in DMF 20ml, were added $NaHCO_3$ (2.52 g) and diphenylmethyl bromide (BH-Br, 2.72 g, 1.1 eq.) under stirring succesively, and the mixture was stirred at 5°C for 16 hr and at room temperature for 8 hr. The reaction mixture was dissolved in AcOEt, washed with water and a saturated brine, dried over Na_2SO_4, and evaporated under reduced pressure. Silica gel chromatograph gave compound 73 (2.55 g, yield 51%).
^{1}H-NMR($CDCl_3$) δ :1.35(9H,S), 1.60(2H,m), 2.67(3H,S), 2.80(3H,S), 2.88(2H,t,J=7.5Hz), 3.04(3H,S), 3.13(2H,m), 6.15 (1H,S), 6.70(1H,dd,J=7.8Hz,4.8Hz), 6.91(1H,dd,J=7.8Hz,1.8Hz), 7.21(10,m), 7.88(1H,dd,J=4.8Hz,1.8Hz), 8.33(1H,S)
IR($CHCl_3$)cm^{-1}:1685,1625,1572,1400

Example 1

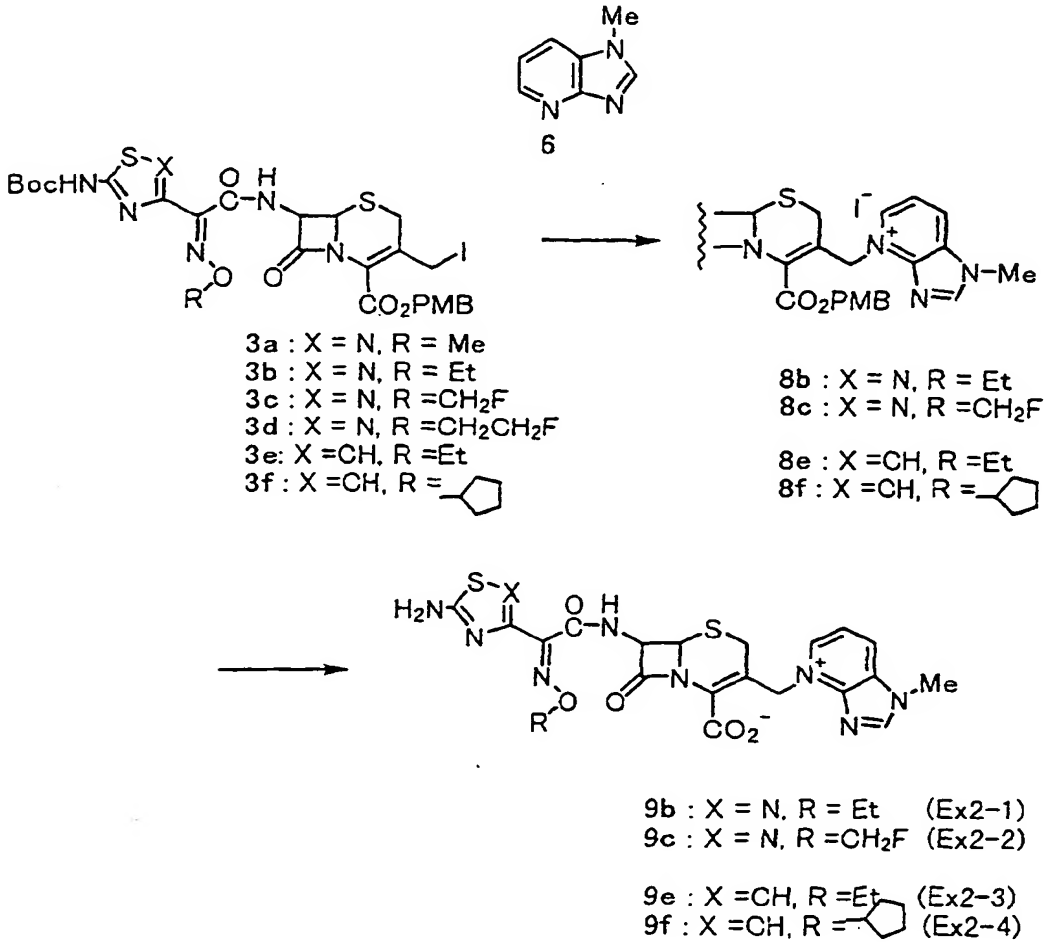
[0162]



(1) To a solution of compound 2 (776 mg, 3.53 mmol) in dried MeCN 5 ml, was added compound 3 (3.21 g, 1.2 eq.) under ice-cooling and the mixture was allowed to stand over night. The resulting mixture was stirred at room temperature for 3 hr and evaporated under reduced pressure to give foamy compound 4b.
(2) To a solution of compound 4b in a mixture of CH_2Cl_2 35 ml, $MeNO_2$ 15 ml, and anisole 10 ml, was added a $AlCl_3$-$MeNO_2$ solution (1.5M, 20 ml) in N2 atmosphere under ice-cooling for 1.5 hr. Ice, 1N HCl, and Et_2O were added thereto, then the water layer was separated, and concentrated under reduced pressure. After HP-20 chromato, the collected portions were lyophilized to give compound 5b (colorless powder, 583 mg).

^{1}H-NMR (D_6-DMSO) δ: 1.18 (3H, t, J = 7.2 Hz), 3.10 and 3.50 (2H, ABq, J = 18 Hz), 4.10 (2H, q, J = 7.2 Hz), 5.12 (1H, d, J = 5.1 Hz), 5.62 (2H, Abq, J = 14.4 Hz), 5.79(1H, dd, J = 5.0 , 8.5 Hz), 7.54 (1H, dd, J = 6.4 , 8.0 Hz), 8.10 (2H, brs), 8.55 (1H, d, J = 5.1 Hz), 8.56 (1H, s), 8.72 (1H, d, J = 6 Hz), 9.53 (1H, d, J = 9 Hz).
IR (KBr) cm^{-1}: 3340, 2983, 1773;1665;1609;1527, 1388; 1037:
Elementary Analysis as $C_{20}H_{19}N_9O_5S_2 \cdot 2.5H_2O$
calc. : C,41.81; H,4.21; N,21.94 (%)
found : C,41.54; H,4.32; N,22.10 (%)

[0163] Reaction schemes of Example 2-1 to Example 2-4 are shown below.



Example 2 - 1

[0164]

(1) To a solution of compound 6 (510 mg, 3.83 mmol) in dried MeCN 5 ml, was added compound 3b (3.34 g, 1.15

eq) under ice-cooling and the mixture was allowed to stand over night, then stirred at room temperature for 1 hr. The mixture was evaporated under reduced pressure to give crystalline compound 8b.
IR (Nujol) cm^{-1}: 3431, 3211, 1773, 1715, 1681, 1636, 1613, 1548, 1246, 1155, 1035
(2) To a solution of compound 8b in a mixture of CH_2Cl_2 40 ml, $MeNO_2$ 30 ml, and anisole 10 ml, was added an $AlCl_3$-$MeNO_2$ solution (1.5 mol, 15 ml) in N_2 atmosphere under ice-cooling and the mixture was stirred for 1.5 hr. Ice, 1N HCl and Et_2O were added thereto, then the water layer was separated, concentrated under reduced pressure, and subjected to HP-20 chromato. The collected eluent was lyophilized to give compound 9b (colorless powder, 1.35 g).
^{1}H-NMR (D_6-DMSO) δ : 1.18 (3H, t, J = 7.2 Hz), 2.95 and 3.52 (2H, ABq, J = 17.4 Hz), 4.06 (3H, s), 4.04 - 4.19 (2H, m), 5.02 (1H, d, J = 5.1 Hz), 5.64 - 5,69 (3H, m), 7.95(1H, dd, J = 6.3, 8.1 Hz), 8.13 (2H, brs), 8.88 (1H, dd, J = 0.9, 8.1 Hz), 9.04 (1H, s), 9.44 (1H, d, J = 8.7 Hz), 9.71(1H, d, J = 5.7 Hz).
IR (KBr) cm^{-1}: 3386, 2984, 1773, 1665, 1636, 1614, 1528, 1389, 1357, 1038.
Elementary Analysis as $C_{21}H_{21}N_9O_5S_2 \cdot 3.6\ H_2O$
calc.: C,41.46 ; H,4.67 ; N,20.72 ; S,10.54
found: C,41.59 ; H,4.79 ; N,20.95 ; S,10.70 (%)

Example 2 - 2

[0165]

(1) To a solution of compound 6 (153 mg, 1.1 mmol) in dried MeCN 2 ml, was added compound 3c (947 mg, 1.3eq) under ice-cooling and the mixture was allowed to stand over night, then stirred at room temperature for 1 hr. The mixture was evaporated under reduced pressure to give crystalline compound 8c.
IR (Nujol) cm^{-1}: 3429, 3211, 1772, 1734, 1714, 1688, 1636, 1549, 1248, 1156, 1121
(2) To a solution of compound 8c in a mixture of CH_2Cl_2 30 ml, MeNO2 30 ml, and anisole 2 ml, was added $TiCl_4$ 0.73 ml in N2 atomosphere atomosphere under ice-cooling and the mixture was stirred for 1.5 hr. Further procedures similar to Example 1(2) gave compound 9c (colorless powder, 254 mg).
^{1}H-NMR (D_6-DMSO) δ: 2.95 and 3.54 (2H, ABq, J = 17.4 Hz), 4.06 (3H, s), 5.03 (1H, d, J = 5.1 Hz), 5.62 - 5.69 (3H, m), 5.71 (1H, d, J = 55.2 Hz),7.95(1H, dd, J = 6.3 , 8.1Hz), 8.18 (2H, brs), 8.87(1H, d, J = 8.4 Hz), 9.03 (1H, s), 9.66 (1H, d, J = 8.4 Hz), 9.72(1H, d, J = 6.3 Hz).
IR (KBr) cm^{-1}: 3398, 2984, 1774, 1671, 1614, 1528, 1394, 1359, 1064, 991 .
Elementary Analysis as $C_{20}H_{18}N_9O_5S_2F \cdot 3.8\ H_2O$
calc. : C,39.00 ; H,4.19 ; N,20.46 ; S,10.43 ; F, 3.09
found : C,39.28 ; H,4.19; N,20.48 ; S,10.43 ; F,2.80 (%)

Example 2 - 3

[0166]

(1) To a solution of compound 6 (90 mg, 0.67 mmol) in dried MeCN 3 ml, was added compound 3e (716 mg, 1.4 eq) under ice-cooling and the mixture was allowed to stand over night, then stirred at room temperature for 1 hr. The reaction mixture was evaporated under reduced pressure to give compound 8e. IR (Nujol) cm^{-1}: 3203, 1784, 1716, 1680, 1549, 1244, 1154, 1030
(2) Compound 8e was deprotected and purified according to 8b, to give compound 9e (colorless powder, 220 mg).

^{1}H-NMR (D_6-DMSO) δ: 1.16 (3H, t, J = 6.9 Hz), 2.98 and 3.54 (2H, ABq, J = 18 Hz), 4.05 (2H, q, J = 7 Hz), 4.07(3H, s), 5.03 (1H, d, J = 4.8 Hz), 5.64 - 5.68 (3H, m), 6.67(1H, s), 7.19 (2H, brs), 7.96(1H, dd, J = 6, 8.4 Hz), 8.88(1H, dd, J = 0.3 , 8.1 Hz), 9.04 (1H, s), 9.46 (1H, d, J = 8.1 Hz), 9.73(1H, dd, J = 0.9, 6.6 Hz). IR (KBr) cm^{-1}: 3398, 2979, 1774, 1662, 1636, 1616, 1535, 1384, 1357, 1038
Elementary Analysis as $C_{22}H_{22}N_8O_5S_2 \cdot 3.8\ H_2O$
calc. : C,43.24 ; H,4.88 ; N,18.34 ; S.10.50
found : C,43.23 ; H,4.94 ; N,18.50 ; S,10.43 (%)

Example 2 - 4

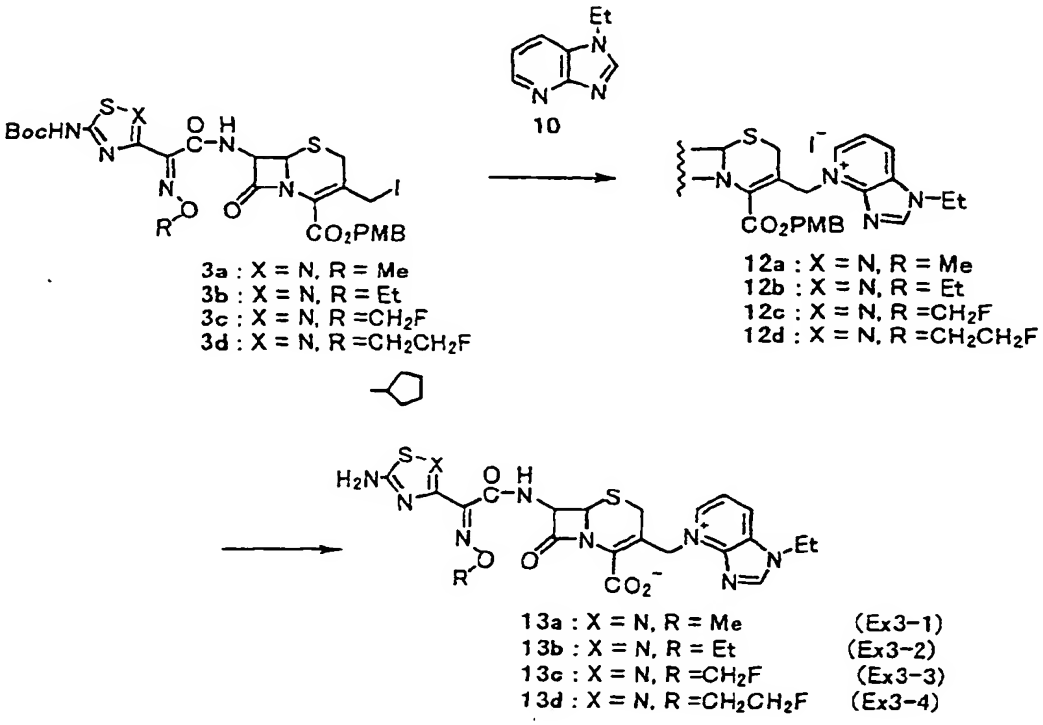
[0167]

(1) To a solution of compound 6 (146 mg, 1.1 mmol) in dried MeCN 7 ml and DMF 2.5 ml, was added compound

3f (1.06 g, 1.25 eq) under ice-cooling and the mixture was allowed to stand over night, then stirred at room temperature for 1 hr. The reaction mixture was evaporated under reduced pressure to give compound 8f.
(2) Compound 8f was deprotected and purified according to 8b, to give compound 9f (colorless powder, 350 mg).

^{1}H-NMR (D_6-DMSO) δ : 1.46 - 1.74 (8H, m), 3.49 (1H, d, J = 19.5 Hz), 4.08 (3H, s), 4.64(1H, m), 4.86 (1H, d, J = 4.8 Hz), 5.70 (2H, m), 5.80(1H, dd, J = 4.5, 8.1 Hz), 6.77(1H, s), 7.18(2H, brs), 7.92(1H, dd, J = 6,3, 8.1 Hz), 8.45 (1H, d, J = 8.4 Hz), 8.89(1H, d, J = 8.1 Hz), 9.02(1H, s), 9.45 (1H, d, J = 6.3 Hz) .
IR (KBr) cm^{-1}:3399, 2957, 2870, 1786, 1617, 1534, 1498, 1348, 1061, 1033, 989. Elementary Analysis as $C_{25}H_{26}N_8O_5S_2 \cdot 4.7\ H_2O$
calc. : C,45.0 ; H,5.35 ; N,16.79 ; S,9.61
found : C,45.01 ; H,5.10 ; N,16.95 ; S,9.76 (%)

[0168] Reaction schemes of Example 3-1 to Example 3-4 are shown below.



Example 3-1

[0169]

(1) To a solution of compound 10 (368 mg, 2.5 mmol) in dried MeCN 5 ml, was added compound 3a (2.33 g, 1.25 eq) under ice-cooling at room temperature and the mixture was stirred for 3 hr. The reaction mixture was evaporated under reduced pressure to give crystalline compound 12a.
IR (Nujol) cm^{-1}: 3448, 3211, 1733, 1714, 1683, 1635, 1613, 1551, 1248, 1156, 1038
(2) To a solution of compound 12a in a miture of CH_2Cl_2 35 ml, $MeNO_2$ 35 ml, and anisole 3 ml, was adde an $AlCl_3$ - $MeNO_2$ solution (1.5M, 10 ml) in N2 atmosphere under ice-cooling and the mixture was stirred for 2.5 hr. Ice, 1N HCl and Et_2O were added thereto, then the water layer was separated, concentrated under reduced pressure, and subjected to HP-20 chromato. The collected eluent was lyophilized to give compound 13a (colorless powder, 641 mg).
^{1}H-NMR (D_6-DMSO) δ : 1.52 (3H, t, J = 7.2 Hz),3.00 and 3.53 (2H, ABq, J = 17.4 Hz), 3.83 (3H, s), 4.51(2H, q, J = 7.5 Hz), 5.01 (1H, d, J = 4.5 Hz), 5.63 - 5.68 (3H, m), 7.95(1H, dd, J = 6.0, 8.4 Hz), 8.11 (2H, brs), 8.94 (1H, dd, J = 0.9, 8.1 Hz), 9.13 (1H, s), 9.46 (1H, d, J = 8.4 Hz), 9.71(1H, d, J = 6.0 Hz).
IR (KBr)cm^{-1}: 3372, 3286, 2984, 2939, 1775, 1668, 1610, 1528, 1387, 1293, 1227, 1040.

Elementary Analysis as $C_{21}H_{21}N_9O_5S_2 \cdot 2.4\ H_2O$
calc. : C,42.98; H,4.43 ; N,21.48 ; S,10.93
found : C,42.99 ; H.4.63 ; N,21.58 ; S,10.65 (%)

Example 3-2

[0170]

(1) To a solution of compound 10 (240 mg, 1.63 mmol) in dried MeCN 1 ml, was added compound 3b (1.50 g, 1.2eq) under ice-cooling and the mixture was stirred at room temperature for 2 hr, then evaporated under reduced pressure to give crystalline compound 12b.
IR (Nujol) cm^{-1}: 3429, 3203, 1773, 1714, 1681, 1634, 1612, 1548, 1245, 1154, 1034
(2) Compound 12b was reacted according to 12a, to give lyophilized powder of compound 13b (630 mg).
^{1}H-NMR (D_6-DMSO) δ : 1.18(3H, t, J = 7.0 Hz), 1.51 (3H, t, J = 7.2 Hz), 2.99 and 3.53 (2H, ABq, J = 17.4Hz), 4.10 (2H, q, J = 6.9 Hz), 4.51(2H, q, J = 7.2 Hz), 5.01 (1H, d, J = 4.5 Hz), 5.66 - 5,69 (3H, m), 7.94(1H, t, J = 6.6 Hz), 8.12 (2H, brs), 8.94 (1H, d, J = 8.1 Hz), 9.12(1H, s), 9.44 (1H, d, J = 8.7 Hz), 9.67(1H, d, J = 6.3 Hz).
IR (KBr) cm^{-1}: 3399, 2938, 1775, 1669, 1634, 1613, 1526, 1385, 1293, 1227, 1038.
Elementary Analysis as $C_{22}H_{23}N_9O_5S_2 \cdot 3.4\ H_2O$
calc. : C,42.70 ; H,4.85 ; N,20.37 ; S,10.24
found : C,42.91 ; H; 5.03 ; N,20.57; S,9.88 (%)

Example 3-3

[0171]

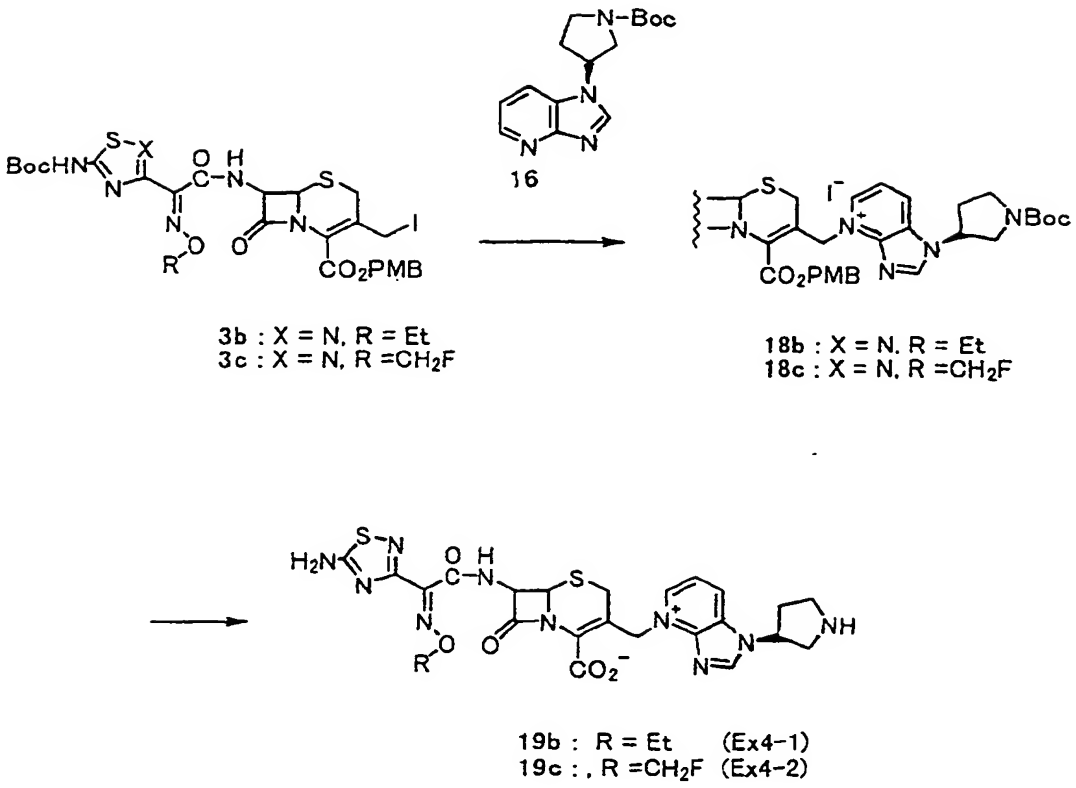
(1) To a solution of compound 10 (368 mg, 2.5 mmol) in dried MeCN 7 ml, was added compound 3c (1.9 g, 1.15 eq) under ice-cooling and the mixture was stirred at room temperature for 3 hr, then allowed to stand at 4°C over night. The reaction mixture was evaporated under reduced pressure to give compound 12c.
IR (Nujol) cm^{-1}:3430, 3209, 1771, 1734, 1713, 1689, 1635, 1613, 1550, 1248, 1156, 1121
(2) Compound 12c was reacted according to Example 2-2(2) by $TiCl_4$ - anisole method, to give lyophilized powder of compound 13c (350 mg).
^{1}H-NMR (D_6-DMSO) δ : 1.52 (3H, t, J = 7.0 Hz), 2.99 and 3.54 (2H, ABq, J = 17.4 Hz), 4.51(2H, q, J = 7.2 Hz), 5.04 (1H, d, J = 4.8 Hz), 5.65 - 5.7 (3H, m), 5.71 (1H, d, J = 55.5 Hz), 7.95(1H, dd, J = 6.0, 8.1Hz), 8.19 (2H, brs), 8.94 (1H, dd, J = 0.9, 8.1 Hz), 9.12(1H, s). 9,65 - 9.71 (2H, m).
IR (KBr) cm^{-1}: 3399, 2983, 1775, 1671, 1613, 1528, 1388, 1080, 991.
Elementary Analysis as $C_{21}H_{20}N_9O_5S_2F \cdot 3.6\ H_2O$
calc. : C,40.27 ; H,4.38; N,20.12 ; S,10.24 ; F,3.03
found : C,40.43 ; H.4.45 ; N,20.23 ; S,9.96 ; F,2.66 (%)

Example 3-4

[0172]

(1) To a solution of compound 10 (368 mg, 2.5 mmol) in dried MeCN 6ml, was added compound 3d (2.5 g, 1.3 eq) under ice-cooling and the mixture was stirred at the same temperature for 1 hr, then allowed to stand over night. The reaction mixture was evaporated under reduced pressure to give compound 12d.
IR (Nujol) cm^{-1}: 3190, 1783, 1714, 1634, 1612, 1546, 1245, 1153
(2) Compound 12d was reacted according to 12c to give lyophilized powder of compound 13d (550 mg).
^{1}H-NMR (D_6-DMSO) δ : 1.51 (3H, t, J = 7.0 Hz), 2.98 and 3.53 (2H, ABq, J = 17.4 Hz), 4.25 (1H, m), 4.35 (1H, m), 4.46 - 4.54 (3H, m), 4.66 (1H, m), 5.02 (1H, d, J = 5.1 Hz), 5.66 - 5.70 (3H, m), 7.94(1H, dd, J = 6.0, 8.1 Hz), 8.13 (2H, brs), 8.94 (1H, d, 8.4 Hz), 9.12(1H, s), 9.52(1H, d, 8.4 Hz), 9.67(1H, d, 6.3 Hz).
IR (KBr) cm^{-1}: 3399, 2984, 1775, 1670, 1612, 1528, 1386, 1292, 1228, 1066.
Elementary Analysis as $C_{22}H_{22}N_9O_5S_2F \cdot 3\ H_2O$
calc. : C.41.97; H,4.48; N, 20.02 ; S, 10.18; F,3.02
found : C,42.22 ; H.4.58 ; N,20.15 ; S, 9.99 ; F,2.73 (%)

[0173] Reaction schemes of Example 4-1 to Example 4-2 are shown below.



3b : X = N, R = Et
3c : X = N, R =CH_2F

18b : X = N, R = Et
18c : X = N, R =CH_2F

19b : R = Et (Ex4-1)
19c : , R =CH_2F (Ex4-2)

Example 4-1

[0174]

(1) To a solution of compound 16 (590 mg, 2 mmol) in dried MeCN 6 ml, was added compound 3b (1.86 g, 1.2eq) under ice-cooling and the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was diluted with Et_2O / EtOH to give crystalline compound 18b (2 g).

IR (Nujol) cm^{-1}: 3424, 3204, 1785, 1714, 1681, 1634, 1612, 1545, 1246, 1155, 1063

(2) To a solution of compound 18b in CH_2Cl_2 30 ml, $MeNO_2$ 35 ml, and anisole 3 ml, was added an $AlCl_3$-$MeNO_2$ solution (2 mol, 12 ml) in N_2 atmosphere under ice-cooling and the mixture was stirred for 2 hr. Ice, 1N HCl and Et_2O were added thereto, then the water layer was separated, concentrated under reduced pressure, and subjected to HP-20 chromato. The portion, eluted with 2% MeCN aq. containing 0.003N HCl, was lyophilized to give hydrochloride of compound 19b (powder, 360 mg).

^{1}H-NMR (D_6-DMSO) δ: 1.19 (3H, t, J = 7.2 Hz), 2.52 - 2.74 (2H, m), 3.12 (1H, d, 18 Hz), 3.67 - 3.8 (2H, m), 4.11 (2H, q, J = 7.2 Hz), 5.06 (1H, d, J = 4.8 Hz), 5.61 - 5.07 (2H, m), 5.75 (1H, dd, J = 4.8, 8.7 Hz), 5.84 (1H, d, J = 14 Hz), 8.00(1H, brt, J = 7.0 Hz), 8.14(2H, brs), 9.09 (1H, brd, J = 8.1 Hz), 9.37 (1H, s), 9.42 (1H, d, J = 5.7 Hz), 9.49(1H, d, J = 8.7 Hz).

^{1}H-NMR (D_2O) δ : 1.30 (3H, t, J = 7.2 Hz), 2.68 - 2.80 (1H, m), 2.85 - 2.97 (1H, m), 3.31 and 3.63(2H, ABq, J = 18 Hz), 3.63 - 3.88 (3H, m), 4.08 - 4.19 (1H, m), 4.33 (2H, q, J = 6.9 Hz), 5.22 (1H, d, J = 4.5 Hz), 5.62 and 5.94 (2H, ABq, J = 14.4 Hz), 5.62 - 5.72 (1H, m), 5.85 (1H, d, J = 4.5 Hz), 7.92(1H, dd, J = 6.3, 8.4 Hz), 8.85(1H, d, J = 8.4 Hz), 8.89 (1H, d, J = 5.7 Hz), 9.03 (1H, s).

IR (KBr) cm^{-1}: 3398, 2982, 1771, 1668, 1611, 1461, 1391, 1037,.

Elementary Analysis as $C_{24}H_{26}N_{10}O_5S_2 \cdot 1.25\ HCl \cdot 4.8\ H_2O$

calc. : C,39.45 ; H.5.08 ; N,19.16 ; S,8.78 ; Cl,6.07

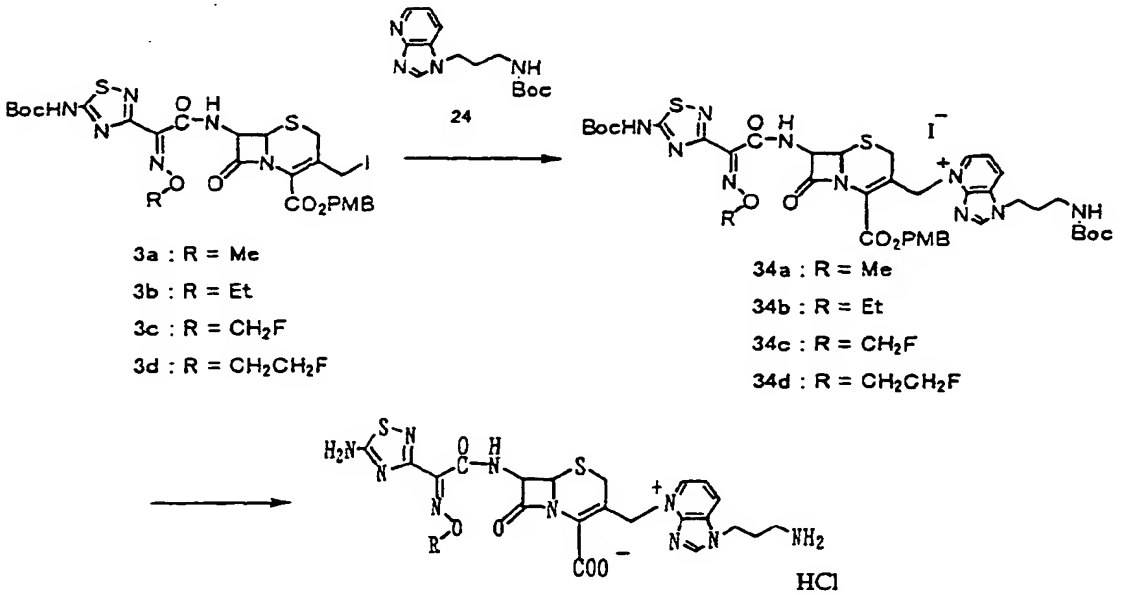
found : C,39.45 ; H.4.95 ; N,19.16 ; S,8.52 ; Cl,6.08 (%)

Example 4-2

[0175]

(1) Compound 16 (355 mg, 1.2 mmol) was reacted according to Example 4-1 to give compound 18c.
IR ($CHCl_3$) cm^{-1}: 3221, 1773, 1717, 1692, 1612, 1153
(2) Compound 18c was reacted according to Example 2-2 to give compound 19c (colorless powder, 31 mg).
^{1}H-NMR (D_2O) δ: 2.67 - 2.77 (1H, m), 2.82 - 2.94(1H, m), 3.30 and 3.63 (2H, ABq, J = 18 Hz), 3.58 - 3.84 (3H, m), 4.03 - 4.10 (1H, m), 5.23 (1H, d, J = 4.8 Hz), 5.61 and 5.96 (2H, ABq, J = 14.4 Hz), 5.61 - 5.72 (1H, m), 5.82 (1H, d, J = 54 Hz),5.87 (1H, d, J = 4.5 Hz), 7.90(1H, dd, J = 6.3, 8.4 Hz), 8.84(1H, d, J = 8.4 Hz), 8.88 (1H, d, J = 6.3 Hz), 9.00 (1H, s).
IR (KBr) cm^{-1}: 3427, 1771, 1671, 1613, 1525, 1462, 1396, 1079, 1064.
Elementary Analysis as $C_{23}H_{23}N_{10}O_5S_2F \cdot 1.15\ HCl \cdot 4.4\ H_2O$
calc. : C,38.16 ; H,4,59 ; N, 19.35 ; S,8.86 ; Cl,5.63; F,2.63
found : C,38.13 ; H,4.62 ; N,19.66 ; S,8.83 ; Cl,5.84; F,2.56 (%)

[0176] Reaction schemes of Example 5-1 to Example 5-4 are shown below.



35a : R = Me (Ex5-1)
35b : R = Et (Ex5-2)
35c : R = CH_2F (Ex5-3)
35d : R = CH_2CH_2F (EX5-4)

Example 5-1

[0177]

(1) To a solution of compound 24 (0.24 g, 0.87 mmol) in MeCN 10ml, was added compound 3a (0.71 g, 1.1 eq.) under stirring at room temperature and the mixture was further stirred for 2 hr. The reaction mixture was concentrated under reduced pressure, then Et_2O 50 ml was added to the residue, followed by filtration to give compound 34a (0.69 g, 78%) as powder.
^{1}H-NMR (DMSO-d6)δ: 1.38(9H, s), 1.50(9H, s), 2.00(2H, m), 2.99(2H, m), 3.40(2H, m), 3.93(3H, s), 4.50(2H, m), 5.09(1H, d, J=4.8 Hz), 5.28(2H, s), 6.09.5.58(2H, ABq, J=14.8 Hz), 5.93(1H, dd, J=8.6 Hz, 4.8 Hz), 6.93(2H, d,

J=8.6 Hz), 7.38(2H, d, J=8.6 Hz), 7.96(1H, dd, J=7.8 Hz, 6.2 Hz), 8.85(1H, d, J=6.2 Hz), 9.01(1H, d, J=7.8 Hz), 9.07(1H, s), 12.6(1H, s)
IR(Nujol)cm^{-1}: 1770,1679,1550,1460
(2) Compound 34a (0.68 g, 0.666 mmol) was dissolved in CH_2Cl_2 12ml and $MeNO_2$ 3ml and the mixture was cooled to -20°C. Anisole (0.87 ml, 10eq.) and an $AlCl_3$-$MeNO_2$ solution (1M, 6.7 ml, 10eq.) were added thereto and the mixture was stirred at -5°C for 1 hr. The reaction mixture was added to a mixture of 0.25N HCl 15ml and Et_2O 30ml under stirring. The water layer was separated, washed with Et_2O 120ml, purified with HP-20. The eluted portion was lyophilized to give compound 35a (0.16g, 37%).
^{1}H-NMR(D_2O) δ : 2.139(2H, m), 3.13(2H, t, J=8.7 Hz), 3.30,3.64(2H, ABq, J=12.1 Hz), 4.05(3H, s), 4.64(2H, t, J=7.2 Hz), 5.22(1H, d, J=4.8 Hz), 5.62,5.89(2H, ABq, J=9.9 Hz), 5.85(1H, d, J=4.8 Hz), 7.88(1H, dd, J=8.1 Hz, 6.3 Hz), 8.80(1H, d, J=8.1 Hz), 8.84(1H, d, J=6.3 Hz), 8.88(1H, s)
IR(KBr)cm^{-1}: 1771,1609,1525,1392

Example 5-2

[0178]

(1) To a solution of compound 24 (0.41 g, 1.48 mmol) in DMF 7ml, was added compound 3b (1.35 g, 1.2eq.) under stirring and ice-cooling and the mixture was stirred at room temperature for 2 hr. The reaction mixture was slowly added to Et_2O 300 ml under stirring, then the precipitate was filtered to give compound 34b (1.46 g, 95%).
^{1}H-NMR(d_6-DMSO)δ: 1.24(3H, t, J=7.2 Hz), 1.38(9H, s), 1.50(9H, s), 2.01(2H, m), 3.30(2H, m), 3.50(2H, m), 3.77 (3H, s), 4.20(2H, q, J=7.2 Hz), 4.50(2H, t, J=7.8 Hz), 5.10(1H, d, J=4.8 Hz), 5.29(2H, s), 6.10,5.58(2H, ABq, J=14.7 Hz), 5.94(1H, dd, J=8.6 Hz. 5.0 Hz), 6.94(2H, d, J=9.0 Hz), 7,38(2H, d, J=8.6 Hz), 7.96(1H, dd, J=8.2 Hz, 5.8 Hz), 8.86(1H, d, J=5.8 Hz), 9.01(1H, d, J=8.2 Hz), 9,07(1H, s), 9.67(1H, d, J=8.6 Hz), 12.59(1H, s)
IR(Nujol)cm^{-1}: 1785,1550,1515,1510,1375
(2) Compound 34b (1.45 g, 1.4 mmol) was dissolved in CH_2Cl_2 28ml and $MeNO_2$ 9ml and the mixture was cooled to -20°C. Anisole (1.83 ml, 12eq.) and an $AlCl_3$-$MeNO_2$ solution (1M, 14 ml, 10eq.) were added thereto at -5°C and the mixture was stirred for 1 hr. The reaction mixture was poured into a mixture of 0.25N HCl 60ml and Et_2O 120ml under stirring. The water layer was separated, washed with Et_2O 120ml, and purified with HP-20. The eluted portion was lyophilized to give compound 35b (0.32 g, 31%).
^{1}H-NMR(D_2O)δ: 1.28(3H, t, J=7.0 Hz), 2.36(2H, m), 3.11(2H, t, J=8.6 Hz), 3.28,3.61(2H, ABq, J=18.0 Hz), 4.615 (2H, t, J=7.0 Hz), 4.30(2H, q, J=7.0 Hz), 5.21(1H, d, J=4.6 Hz), 5.60, 5.87(2H, ABq, J=14.7 Hz), 7.86(1H, dd, J =8.2 Hz, 6.2 Hz), 8.78(1H, d, J=8.2 Hz), 8.81(1H, d, J=6.2 Hz),8.85(1H, s)
IR(KBr)cm^{-1}: 1772,1615,1524,1387
Elementary Analysis as $C_{23}H_{26}N_{10}O_5S_2 \cdot 1.3HCl \cdot 4.1H_2O$
calc. : C,39.02; H,5.05; N,19.79; S,9.06; Cl,6.51
found: C,39.04; H,5.10; N,19.46; S,9.08; Cl,6.53

Example 5-3

[0179]

(1) To a solution of compound 24 (0.71 g, 2.57 mmol) in DMF 10ml, was added compound 3c (2.35 g, 1.2eq.) under stirring and ice-cooling and the mixture was stirred at room temperature for 1 hr. The reaction mixture was slowly added to Et_2O 500ml under stirring, then the precipitate was filtered to give compound 34c (2.79 g).
^{1}H-NMR(d6-DMSO) δ : 1.38(9H, s), 1.51(9H, s), 2.0(2H, m), 2.98(2H, m), 3.48(2H, m), 3.77(3H, s), 4.50(2H, t, J=7.8Hz), 5.12(1H, d, J=5 Hz), 5.28(2H, s), 6.09,5.59(2H, ABq, J=14.6 Hz), 5,82(2H, d, J=55.6 Hz), 5.95(1H, m), 6.93(2H, d, J=9 Hz), 7.38(2H, d, J=9 Hz), 7.95(1H, dd, J=7.8 Hz, 5.8 Hz), 8.85(1H, d, J=5.8 Hz), 9.01(1H, d, J=7.8 Hz), 9.08(1H, s),12.7(1H, s)
IR(Nujol)cm^{-1}: 1785,1545,1515,1459,1375
(2) Compound 34c (2.78 g, 2.68 mmol) was dissolved in CH_2Cl_2 50 ml and $MeNO_2$ 25 ml and the mixture was ice-cooled. Anisole (3.49 ml, 12eq.) and $TiCl_4$ (2.94 ml, 10eq.) were added thereto under stirring at 5°C for 1 hr. The reaction mixture was poured into 0.25N HCl 150ml and Et_2O 300ml. The water layer was separated, washed with Et_2O 300ml, and purified with HP-20. The eluted portion was lyophilized to give compound 35c (0.62 g, 33%).
^{1}H-NMR(D_2O) δ: 2.38(2H, m), 3.13(2H, t, J=8.4 Hz), 3.28,3.64(2H, ABq, J=17.9 Hz), 4.63(2H, t, J=7.0 Hz),5.23 (1H, d, J=4.8 Hz),5.60.5.87(2H, ABq, J=14.7 Hz),5.82(2H, d, J=54.6 Hz), 7.86(1H, dd, J=8.2 Hz, 6.2 Hz),8.78(1H, d, J=8.2 Hz),8.82(1H, d, J=6.2 Hz), 8.87(1H, s)
IR(KBr)cm^{-1}:1773,1614,1525,1390

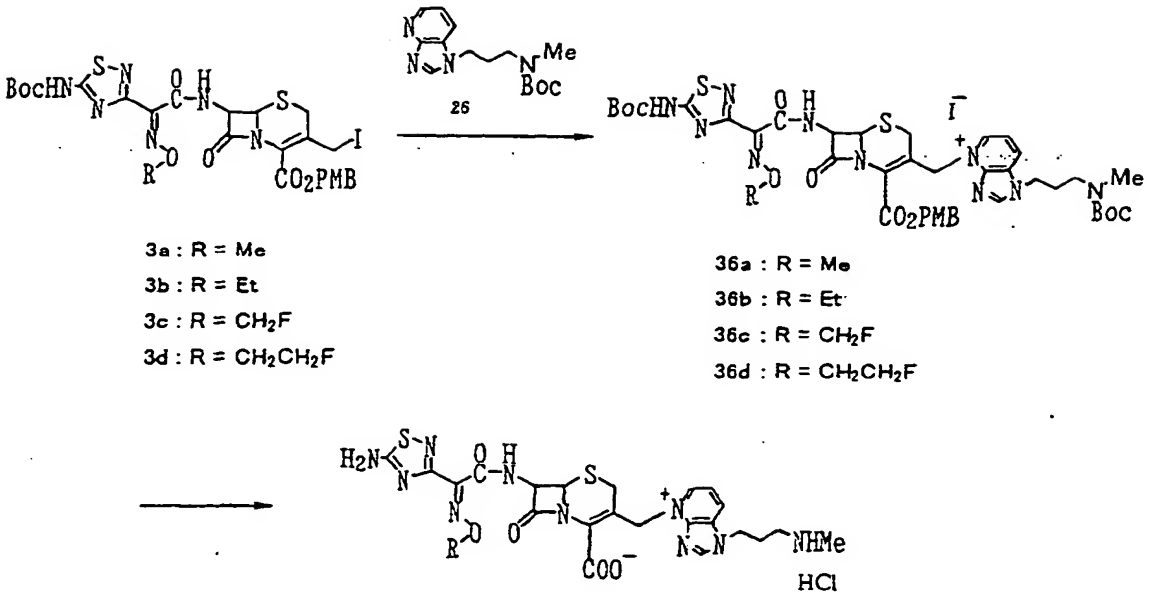
Elementary Analysis as $C_{22}H_{23}N_{10}O_5S_2F \cdot 1.2\ HCl \cdot 3.6H_2O$
calc. : C,37.79; H,4.53; N,20.03; S,9.17; F,2.72; Cl,6.08
found: C,37.76; H,4.61; N,20.22; S,8.89; F,2.56; Cl,6.00

Example 5-4

[0180]

(1) To a solution of compound 24 (0.28 g, 1.01 mmol) in MeCN 10ml, was added compound 3d (1.02 g, 1.3eq.) under stirring at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure, then Et_2O 50ml was added to the residue, followed by filtration to give compound 34d (1.19 g) as powder.
^{1}H-NMR(d_6-DMSO) δ: 1.38(9H, s), 1.51(9H, s), 2.00(2H, m), 2.97(2H, m), 3.50(2H, m), 3.77(3H, s), 4.30(2H, m), 4.50(4H, m), 4.85(2H, m), 5.12(1H, d, J=4.6 Hz), 6.11,5.58(2H, ABq, J=14.2 Hz), 5.94(1H, m), 6.94(2H, d, J=8.6 Hz), 7.38(2H, d, J=8.6 Hz), 7.95(1H, dd, J=7.8 Hz, 6.2 Hz), 8.86(1H, d, J=6.2 Hz), 9.01(1H, d, J=7.8 Hz), 9.07(1H, s), 9.74(1H, d, J=8.6 Hz), 12.6(1H, s)
IR(Nujol)cm^{-1}: 1785,1610,1540,1510,1375
(2) Compound 34d (1.1 g, 1.04 mmol) was dissolved in CH_2Cl_2 18 ml and $MeNO_2$ 10ml and the mixture was ice-cooled. Anisole (1.36 ml, 12eq.) and $TiCl_4$ (1.15 ml, 10eq.) were added thereto at 5°C and the mixture was stirred for 1 hr. The reaction mixture was poured into 0.25N HC 125ml and Et_2O 50ml with stirring. The water layer was separated, washed with Et_2O 300ml, and purified with HP-20. The eluted portion was lyophilized to give compound 35d (0.17 g, 23%).
^{1}H-NMR(D_2O) δ: 2.38(2H, m), 3.13(2H, t, J=8.2 Hz), 3.30,3.63(2H, ABq, J=18.0 Hz), 4.70(6H, m),5.23(1H, d, J=5.0 Hz),5.62,5.90(2H, ABq, J=14.3 Hz),5.85(1H, d, J=5.0 Hz),7.88(1H, dd, J=8.2 Hz, 6.6 Hz),8.80(1H, d, J=8.2 Hz), 8.84(1H, d, J=6.6 Hz),8.88(1H, s)
Elementary Analysis as $C_{23}H_{25}N_{10}O_5S_2F \cdot 1.1\ HCl \cdot 4.5H_2O$
calc. :C,38.06; H,4.87; N,19.30; S,8.84; F,2.62; C1,5.37
found :C,38.02; H,4.86; N,19.16; S,8.65; F,2.41; Cl,5.46

[0181] Reaction schemes of Example 6-1 to Example 6-4 are shown below.



3a : R = Me
3b : R = Et
3c : R = CH_2F
3d : R = CH_2CH_2F

36a : R = Me
36b : R = Et
36c : R = CH_2F
36d : R = CH_2CH_2F

37a : R = Me (Ex6-1)
37b : R = Et (Ex6-2)
37c : R = CH_2F (Ex6-3)
37d : R = CH_2CH_2F (EX6-4)

Example 6 - 1

[0182]

(1) To a solution of compound 26 (0.59 g, 2.03 mmol) in MeCN 15ml, was added compound 3a (1.66 g, 1.1eq.) under stirring at room temperature and the mixture was further stirred for 1.5 hr. Et_2O 80ml was added to the reaction mixture, then the precipitate was filtered to give compound 36a (1.67 g, yield:79%).
^{1}H-NMR(d6-DMSO) δ : 1.36(9H, s), 1.50(9H, s), 2.10(2H, m), 2.80(2H, s), 3.23(2H, m),3.45(2H, m),3.77(3H, s), 3.93(3H, s),4.45(2H, m),5.09(1H, d, J=5.2 Hz),5.29(2H, s),5.59,6.09(2H, ABq, J=14.6 Hz),5.93(1H, dd, J=8.6 Hz, 5.2 Hz),6.93(2H, d, J=8.6 Hz),7.38(2H, d, J=8.6 Hz),7.95(1H, dd, J=7.8 Hz, 6.2 Hz),8.86(1H, d, J=6.2 Hz),9.04 (1H, d, J=7.8 Hz),9.10(1H, s),9.74(1H, d, J=8.6 Hz),12.6(1H, s)
IR(Nujol)cm^{-1}: 1770,1710,1680,1550,1460,1375
(2) Compound 36a (1.65 g, 1.59 mmol) was dissolved in CH_2Cl_2 30 ml and $MeNO_2$ 8 ml and the mixture was cooled to -20°C. Anisole (2.08 ml, 12eq.) and an $AlCl_3$-$MeNO_2$ solution (1M, 15.9 ml, 10eq.) were added thereto and the mixture was stirred at -5°C for 1 hr. The reaction mixture was poured into a mixture of 0.25N HCl 35ml and Et_2O 70ml with stirring. The water layer was separated, washed with Et_2O 120ml, and purified with HP-20. The eluted portion was lyophilized to give compound 37a (0.43 g, 39%).
^{1}H-NMR(D_2O) δ : 2.40(2H, m), 2.73(3H, s), 317(2H, t, J=8.2 Hz), 3.30, 3.64(2H, ABq, J=17.9 Hz), 4.05(3H, s), 4.64(2H, t, J=7.0 Hz), 5.22(1H, d, J=4.8 Hz), 5.62,5.89(2H, ABq, J=14.6 Hz),5.85(1H, d, J=4.8 Hz),7.88(1H, dd, J=8.6 Hz, 6.6 Hz),8.80(1H, d, J=8.6 Hz),8.84(1H, d, J=6.6 Hz),8.88(1H, s)
IR(KBr)cm^{-1}: 1773,1669,1611,1525,1389
Elementary Analysis as $C_{23}H_{26}N_{10}O_5S_2 \cdot 1.1HCl \cdot 3.9H_2O$
calc, : C,39.63; H,5.05; N,20.10; S,9.20; Cl,5.59
found :C,39.68; H,5.07; N,20.31; S,9.27; C1,5.40

Example 6-2

[0183]

(1) To a solution of compound 26 (0.54 g, 1.86 mmol) in DMF 8ml, was added compound 3b (1.69 g, 1.2eq.) under stirring and ice-cooling and the mixture was stirred at room temperature for 1 hr. The reaction mixture was slowly added to Et_2O 300 ml under stirring, then the precipitate was filtered to give compound 36b (1.90 g, 96%).
^{1}H-NMR(d6-DMSO)δ : 1.23(3H, t, J=7.0 Hz), 1.36(9H, s),1.51(9H, s), 2.18(2H, m), 2.80(3H, s),3.45(2H, m),3.77 (3H, s),4.20(2H, q, J=7.0 Hz),4.47(2H, m),5.10(1H, d, J=5.2 Hz),5.29(2H, s),6.10,5.59(2H, ABq, J=14.3 Hz),5,95 (1H, dd, J=8.4 Hz, 5.2 Hz),6.93(2H, d, J=8.8 Hz),7.39(2H, d, J=8.8 Hz),7.95(1H, dd, J=7.6 Hz, 6.4 Hz),8.86(1H, d, J=6.4 Hz),9.04(1H, d, J=7.6 Hz),9.10(1H, s),9.67(1H, s),12.59(1H, s)
IR(Nujol)cm^{-1}: 1790,1715,1545,1460,1380
(2) Compound 36b (1.89 g, 1.8 mmol) was dissolved in CH_2Cl_2 36 ml and $MeNO_2$ 12 ml and the mixture was cooled to -20°C. Anisole (2.35 ml, 12eq.) and an $AlCl_3$-$MeNO_2$ solution (1M, 18 ml, 10eq.) were added thereto and the mixture was stirred at -5°C for 1 hr. The reaction mixture was poured into a mixture of 0.25N HCl 80ml and Et_2O 160ml, then the water layer was separated, washed with Et_2O 120 ml, and purified with HP-20. The eluted portion was lyophilized to give compound 37b (0.40 g, 31%).
^{1}H-NMR(D_2O)δ: 1.31(3H, t, J=7.2 Hz), 2.41(2H, m), 2.73(3H, s), 3.17(2H, t, J=8.4 Hz),3.31,3.64(2H, ABq, J=18.2 Hz),4.32(2H, q, J=7.2 Hz),4.64(2H, t, J=7.5 Hz),5.24(1H, d, J=5.1 Hz),5.64,5.90(2H, ABq, J=14.7 Hz),5.85(1H, d, J=5.1 Hz).7.89(1H, dd, J=8.4 Hz, 6.3 Hz),8.80(1H, d, J=8.4 Hz),8.85(1H, d, J=6.3 Hz),8.88(1H, s)
IR(KBr)cm^{-1}:1774,1616,1525,1387
Elementary Analysis as $C_{24}H_{28}N_{10}O_5S_2 \cdot 1.3HCl \cdot 4.1H_2O$
calc. :C,39.93; H,5.24; N,19.40; S,8.88; Cl,6.38
found :C,39.90; H,5.15; N,19.37; S,8.84; Cl,6.59

Example 6-3

[0184]

(1) To a solution of compound 26 (0,63 g, 2.17 mmol) in DMF 8 ml, was added compound 3c (1.99 g, 1.2eq.) under stirring and ice-cooling and the mixture was stirred at room temperature for 1 hr. The reaction mixture was slowly added to Et_2O 500ml under stirring, then the precipitate was filtered to give compound 36c (2.42 g).
^{1}H-NMR(DMSO-d6) δ: 1.36(9H, s), 1.51(9H, s), 2.18(2H, m), 2.80(3H, s), 3.30(2H, m), 3.50(2H, m), 3.77(3H, s), 4.48(2H, t, J=7.8 Hz), 5.13(1H, d, J=4.9 Hz), 5.29(2H, s), 6.11, 5.60(2H, ABq, J=14.3 Hz), 5.81(2H, d, J=55.3 Hz), 5.95(1H, m), 6.93(2H, d, J=8.8 Hz), 7.38(2H, d. J=8.8 Hz), 7.96(1H, dd, J=8.0 Hz, 6.0 Hz), 8.87(1H. d, J=6.0 Hz), 9.05(1H, d, J=8.0 Hz), 9.11(1H, s), 9.87(1H, s), 12.7(1H, s)
IR(Nujol)cm^{-1}: 1785,1710,1545,1460,1245
(2) Compound 36c (2.37 g, 2.25 mmol) was dissolved into CH_2Cl_2 40ml and $MeNO_2$ 20ml and the mixture was ice-cooled. Anisole (2.94 ml, 12eq.) and $TiCl_4$ (2.47 ml, 10eq.) were added thereto and the mixture was stirred at 5°C for 1 hr. The reaction mixture was poured into 0.25N HCl 120ml and Et_2O 240 ml, then the water layer was separated, washed with Et_2O 300ml, and purified with HP-20. The eluted portion was lyophilized to give hydrochloride of compound 37c (0.50 g, yield:31%).
^{1}H-NMR(D_2O)δ: 2.40(2H, m), 2.73(3H, s), 317(2H, t, J=8.2 Hz), 3.29, 3.64(2H, ABq, J=18.0 Hz), 4.63(2H, t, J=7.2 Hz), 5.24(1H. d, J=4.6 Hz), 5.63, 5.90(2H, ABq, J=14.2 Hz), 5.82(2H, d, J=54.2 Hz), 5.86(1H, d, J=4.6 Hz), 7.87 (1H, dd, J=8.2 Hz, 6.2 Hz), 8.79(1H, d, J=8.2 Hz), 8.85(1H, d, J=6.2 Hz), 8.87(1H, s)
IR(KBr)cm^{-1}: 1774,1671,1617,1525,1393
Elementary Analysis as $C_{23}H_{25}N_{10}O_5S_2F \cdot 1.4HCl \cdot 4.1H_2O$
calc. :C,37.87; H,4.78; N,19.20; S,8.79; F,2.60; Cl,6.80
found :C.37.82; H,4.76; N,19.35; S,8.60; F,2.80; Cl,6.66

Example 6-4

[0185]

(1) To a solution of compound 26 (0.66 g, 2.27 mmol) in MeCN 5ml, was added a solution of compound 3d (2.29 g, 1.3eq.) in MeCN 10ml at room temperature under stirring and the mixture was stirred for 1.5 hr. The reaction mixture was concentrated under reduced pressure and Et_2O 70 ml was added to the residue, followed by filtering to give compound 36d (2.65 g) as powder.

^{1}H-NMR(DMSO-d6) δ : 1.36(9H, s), 1.50(9H, s), 2.15(2H, m), 2.80(3H, s), 3.23(2H, m), 3.45(2H, m), 3.77(3H, s), 4.35(2H, m), 4.50(4H, m), 5.09(1H, d, J=5.2 Hz), 5.29(2H, s), 6.11, 5.59(2H, ABq, J=13.9 Hz), 5.95(1H, dd, J=8.6 Hz, 5.2 Hz), 6.94(2H, d, J=8.6 Hz), 7.38(2H d, J=8.6 Hz), 7.96(1H, dd, J=8.2 Hz, 5.8 Hz), 8.86(1H, d, J=5.8 Hz), 9.04(1H, d, J=8.2 Hz), 9.10(1H, s), 9.74(1H, d, J=8.6 Hz), 12.62(1H, s)

IR(Nujol)cm^{-1}: 1782,1710,1680,1545,1515,1460

(2) Compound 36d (2.65 g, 2.48 mmol) was dissolved in CH_2Cl_2 45ml and $MeNO_2$ 20ml and the mixture was ice-cooled. Anisole (3.24 ml, 12eq.) and $TiCl_4$ (2.73 ml, 10eq.) were added thereto and the mixture was stirred at 5°C for 1 hr. The reaction mixture was poured into 0.25N HCl 60ml and Et_2O 120ml under stirring. The water layer was separated, washed with Et_2O 300 ml, and purified with HP-20. The eluted portion was lyophilized to give compound 37d (0.48 g, 26%).

^{1}H-NMR(D_2O)δ: 2.43(2H, m), 2.75(3H, s), 319(2H, t, J=8.4 Hz), 3.32, 3.65(2H, ABq, J=18.0 Hz), 4.66(6H, m), 5.26 (1H, d, J=5.1 Hz), 5.65, 5.92(2H, ABq, J=14.6 Hz), 5.87(1H, d, J=5.1 Hz), 7.90(1H, dd, J=8.4 Hz, 6.9 Hz), 8.81 (1H, d, J=8.4 Hz), 8.87(1H, d, J=6.3 Hz), 8.89(1H, s)

IR(KBr)cm^{-1}: 1774,1671,1615,1526,1387

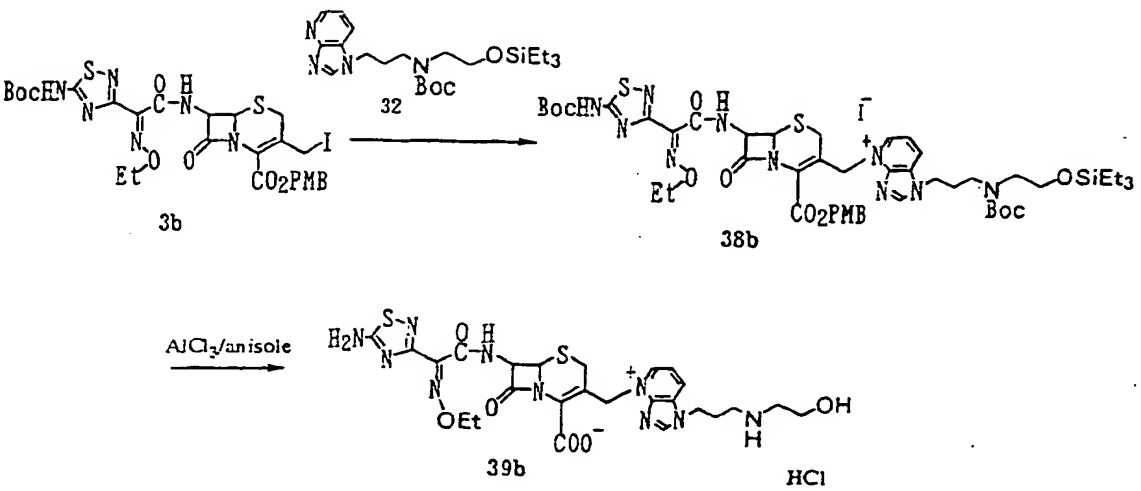
Elementary Analysis as $C_{24}H_{27}N_{10}O_5S_2F\cdot1.1HCl\cdot4.0H_2O$

calc. : C,39.44; H,4.99; N,19.17; S,8.77; F,2.60; Cl,5.34

found :C,39.46; H,5.02; N,19.48; S,8.71; F,2.56; Cl,5.36

Exampie 7

[0186]



(1) To a solution of compound 32 (0.78 g, 1.79 mmol) in MeCN 17ml, was added compound 3b (1.50 g, 1.1eq.) under stirring at room temperature and the mixture was stirred for 1.5 hr. The reaction mixture was concentrated under reduced pressure and Et_2O 80 ml was added to the residue, followed by filtration to give compound 38b (1.77 g, 83%) as powder.

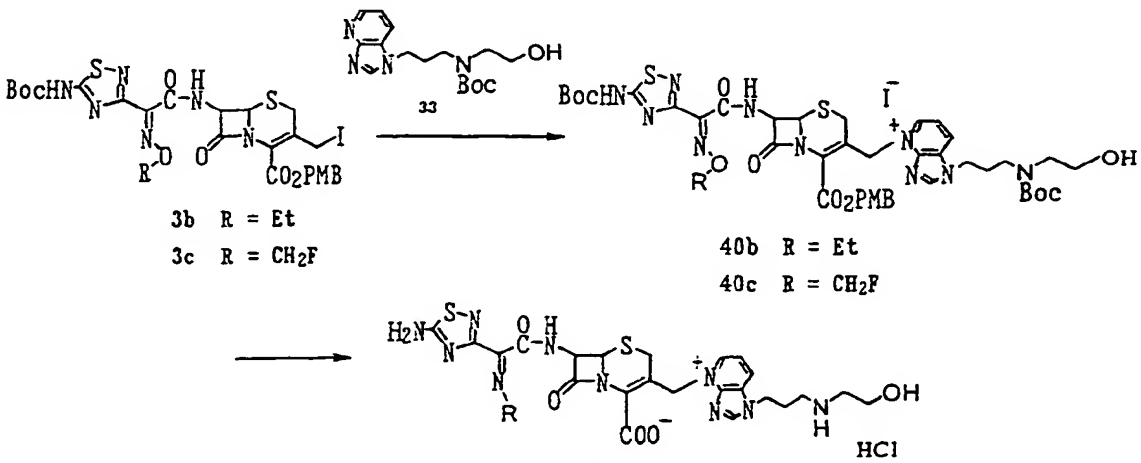
^{1}H-NMR(d6-DMSO)δ: 0.54(6H, q, J=8.1 Hz), 0.89(9H, t, J=8.1 Hz), 1.24(3H, t, J=6.9 Hz), 1.38(9H, s), 1.51(9H, s), 2.10(2H, m), 3.25(8H, m), 3.60(2H, m), 3.76(3H, s), 4.20(2H, q, J=6.9 Hz), 4.45(2H, m), 5.10(1H, d, J=4.8 Hz), 5.29(2H, s), 5.59, 6.10(2H, ABq, J=14.4 Hz), 5.94(1H, dd, J=8.4 Hz, 4.8 Hz), 6.94(2H, d, J=8.7 Hz), 7.38(2H, J=8.7 Hz), 7.96(1H, dd, J=9.0 Hz, 5.4 Hz), 8.86(1H; d, J=5.4 Hz), 9.04(1H, d, J=9.0 Hz), 9.10(1H, s), 9.67(1H, d, J=8.4 Hz), 12,59(1H, s)

IR(Nujol)cm^{-1}: 1770,1710,1680,1540,1455,1370

(2) Compound 38b (1.75 g, 1.47 mmol) was dissolved in CH_2Cl_2 28 ml and $MeNO_2$ 7 ml and the mixture was cooled to -20°C. Anisole (1.91 ml, 12eq.) and an $AlCl_3$-$MeNO_2$ solution (1M, 14.7 ml, 10eq.) were added thereto and the mixture was stirred at -5°C for 1 hr. The reaction mixture was poured into a mixture of 0.25N HCl 35 ml and Et_2O 70 ml, then the water layer was separated, washed with Et_2O 120 ml, and purified with HP-20. The eluted portion was lyophilized to give compound 39b (0.13 g, 12%).

^{1}H-NMR(D_2O) δ : 1.30(3H, t, J=6.9 Hz), 2.42(2H, m), 3.22(4H, m), 3.31, 3.64(2H, ABq, J=18.2 Hz), 3.83(2H, t, J=5.4 Hz), 4.33(2H, q, J=6.9 Hz), 4.65(2H, t, J=6.6 Hz), 5.23(1H, d, J=4.8 Hz), 5.62, 5.90(2H, ABq, J=14.6 Hz), 5.86(1H, d, J=4.8 Hz), 7.89(1H, dd, J=8.1 Hz, 6.6 Hz), 8.80(1H, d, J=8.1 Hz), 8.84(1H, d, J=6.6 Hz), 8,88(1H, s)
IR(KBr)cm^{-1}: 1773,1669,1611,1527,1388
Elementary Analysis as $C_{25}H_{30}N_{10}O_6S_2 \cdot 1.1HCl \cdot 5.2H_2O$
calc. C,39.27; H,5.48; N,18.32; S,8.39; Cl,5.10
found C,39.24; H,5.59; N,18.13; S,8.39; Cl,5.32

[0187] Reaction schemes of Example 8-1 to Example 8-2 are shown below.



Example 8-1

[0188]

(1) To a solution of compound 33 (1.9g, 5.93 mmol) in MeCN 57 ml, was added a solution of compound 3b (4.95g, 1.1eq.) in MeCN 20ml at room temperature and the mixture was stirred for 3 hr. The reaction mixture was concentrated under reduced pressure and the residue was added to $(i\text{-}Pr)_2O$ 500 ml under stirring, then the precipitate was filtered to give compound 40b (6.07 g, 95%).
^{1}H-NMR(d_6-DMSO)δ: 1.24(3H, t, J=6.8 Hz), 1.36(9H, s), 1.51(9H, s), 2.12(2H, m), 3.35(8H, m), 3.77(3H, s), 4.20 (2H, q, J=6.8 Hz), 4.45(2H, m), 5.10(1H, d, J=4.9 Hz), 5.29(2H, s), 5.59, 6.11(2H, ABq, J=14.5 Hz), 5.94(1H, dd, J=8.4 Hz, 4.9 Hz), 6.94(2H, d, J=8.8 Hz), 7.38(2H, d, J=8.8 Hz), 7.95(1H, dd, J=7.7 Hz, 6.2 Hz), 8.86(1H, d. J=6.2 Hz), 9.03(1H. d, J=7.7 Hz), 9.10(1H, s), 9.66(1H, d, J=8.4 Hz), 12.58(1H, s)
IR(Nujol)cm^{-1}: 1790,1715,1545,1460,1380
(2) Compound 40b (6.05 g, 5.6 mmol) was dissolved in CH_2Cl_2 120 ml and $MeNO_2$ 86 ml and the mixture was cooled to -20°C. Anisole (7.30 ml, 12eq.) and an $AlCl_3$-$MeNO_2$ solution (1M, 56 ml, 10eq.) were added thereto and the mixture was stirred at -5°C for 1 hr. The reaction mixture was poured into 0.25N HCl 120 ml and Et_2O 240 ml under stirring. The water layer was separated, washed with Et_2O 120 ml, and purified with HP-20. The eluted portion was lyophilized to give compound 39b (1.81 g, 42%). The physical data was identical to that of Example 7.

Example 8-2

[0189]

(1) To a solution of compound 33 (0.70 g, 2.2 mmol) in MeCN 30ml, was added a solution of compound 3c (1.85 g, 1.1eq.) in MeCN 7 ml under stirring at room temperature, and the mixture was stirred for 3 hr. The reaction mixture was concentrated under reduced pressure and the residue was added to $i\text{-}Pr_2O$ 200ml under stirring, then the precipitate was filtered to give compound 40c (2.01 g, 84%).

^{1}H-NMR(d6-DMSO) δ: 1.36(9H, s), 1.51(9H, s), 2.12(2H, m), 3.35(8H, m), 3.77(3H, s), 4.47(2H, m), 5.12(1H, d, J=4.9 Hz), 5.29(2H, s), 5.60, 6.11(2H, ABq, J=14.3 Hz), 5.81(2H, d, J=55.0 Hz), 5.96(1H, m), 6.94(2H, d. J=8.6 Hz), 7.38(2H, d, J=8.6 Hz), 7.90(1H, dd, J=8.2 Hz, 6.3 Hz), 8.86(1H, d, J=6.3 Hz), 9.013(1H, d, J=8.2 Hz), 9.10 (1H, s), 9.87(1H, d, J=8.2 Hz),12.65(1H, s)

IR(Nujol)cm^{-1}: 1785,1710,1545,1460,1245

(2) Compound 40c (2.01 g, 1.86 mmol) was dissolved in CH_2Cl_2 34 ml and $MeNO_2$ 17 ml and the mixture was ice-cooled. Anisole (2.4 ml, 12eq.) and $TiCl_4$ (2.0 ml, 10eq.) were added thereto and the mixture was stirred at 5°C for 1 hr. The reaction mixture was poured into 0.25N HCl 40 ml and Et_2O 90 ml, then the water layer was separated, washed with Et_2O 300 ml, and purified with HP-20. The eluted portion was lyophilized to give compound 39c (0.49 g, 35%).

^{1}H-NMR(D_2O)δ: 2.44(2H, m), 3.22(4H, m), 3.30, 3.65(2H, ABq, J=16.0 Hz), 3.84(2H, t, J=7.1 Hz), 4.65(2H, t, J=5.7 Hz), 5.25(1H, d, J=4.7 Hz), 5.63, 5,89(2H, ABq, J=15.3 Hz), 5.84(2H, d, J=54.2 Hz), 5.87(1H, d, J=4.7 Hz), 7.89 (1H, dd, 8.2 Hz, 6.4 Hz), 8.80(1H, d, J=8.2 Hz), 8.86(1H, d, J=6.4 Hz). 8.88(1H, s)

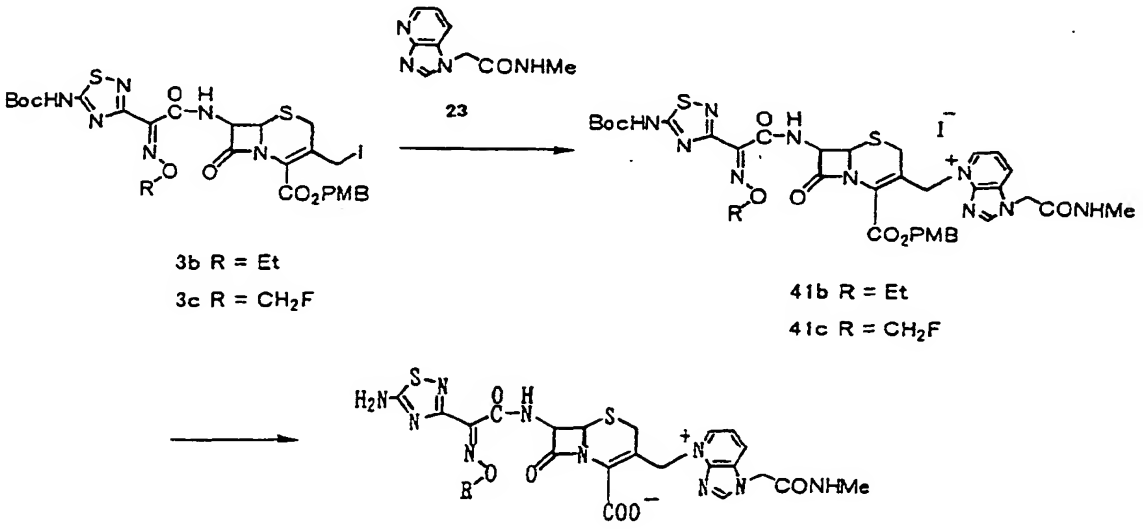
IR(KBr)cm^{-1}: 1778,1675,1616,1525,1386

Elementary Analysis as $C_{24}H_{27}N_{10}O_6S_2F \cdot 1.1HCl \cdot 4.0H_2O$

calc. : C,38.60; H,4.87; N,18.75; S,8.59; F,2.54; Cl,5.22

found : C,38.67; H,4.84; N,18.57; S,8.24; F,2.37; Cl,5.13

[0190] Reaction schemes of Example 9-1 to Example 9-2 are shown below.



Example 9-1

[0191]

(1) To a solution of compound 23 (247 mg, 1.3 mmol) in DMF 7 ml, was added compound 3b (1.28 g, 1.3eq.) under stirring and ice-cooling and the mixture was stirred at room temperature for 1 hr. The reaction mixture was slowly added to Et_2O 400 ml under stirring, then the precipitate was filtered to give compound 41b (1.32 g).

^{1}H-NMR(d_6-DMSO) δ:1.24(3H, t, J=7.0 Hz), 1.51(9H, s), 2.68(3H, d, J=4.6 Hz), 3.54(2H, m), 3.77(3H, s), 4.20(2H, q, J=7.0 Hz), 5.15(1H, d, J=5.0 Hz), 5.27(2H, s), 5.59, 6.14(2H, ABq, J=14.8 Hz), 5.93(1H, dd, J=8.2 Hz, 5.0 Hz), 6.93(2H, d, J=8.6 Hz), 7.37(2H, d, J=8.6 Hz), 7.96(1H, dd, J=9.0 Hz, 5.6 Hz), 8.38(1H, d, J=9.0 Hz), 8.87(1H, d, J=5.6 Hz), 9.00(1H, s), 9.68(1H, d, J=8.2 Hz), 12.59(1H, s)

IR(Nujol)cm^{-1}: 1785,1715,1680,1550,1460

(2) Compound 41b (1.31 g, 1.38 mmol) was dissolved in CH_2Cl_2 28 ml and $MeNO_2$ 9 ml and the mixture was cooled to -20°C. Aanisole (1.8 ml, 12eq) and an $AlCl_3$-$MeNO_2$ solution (1M, 13.8 ml, 10eq) were added thereto

and the mixture was stirred at -5°C for 1 hr. The reaction mixture was poured into 0.25N HCl 70 ml and Et_2O 140 ml with stirring. The water layer was separated, washed with Et_2O 120 ml and purified with HP-20. The eluted portion was lyophilized to give compound 42b (0.45 g, 49%).

^{1}H-NMR(D_2O) δ : 1.29(3H, t, J=7.0 Hz), 2.81(3H, s), 3.28, 3.61(2H, ABq, J=18.1 Hz), 4.31(2H, q, J=7.0 Hz), 5.22 (1H. d, J=5.0 Hz), 5.34(2H, s), 5.67, 5.91(2H, ABq, J=14.8 Hz), 5.86(1H, d, J=5.0 Hz), 7.88(1H, dd, J=8.0 Hz, 6.2 Hz), 8.66(1H. d, J=8.0 Hz), 8.83(1H, s),8.90(1H, d, J=6.2 Hz)

IR(KBr)cm^{-1}: 1773,1673,1613,1385

Elementary Analysis as $C_{23}H_{24}N_{10}O_6S_2 \cdot 3.7H_2O$

calc. : C,41.40; H,4.74; N,20.99; S,9.61

found : C,41.37; H,4.69; N,21.34; S,9.56

Example 9 - 2

[0192]

(1) To a solution of compound 23 (476 mg, 2.5 mmol) in DMF 10 ml, was added compound 3c (2.29 g, 1.2eq) under stirring and ice-cooling and the mixture was stirred at room temperature for 1 hr. The reaction mixture was slowly added to Et_2O 500 ml, then the precipitate was filtered to give compound 41c (2.81 g).

^{1}H-NMR(d_6-DMSO) δ :1.51(9H, s), 2.68(3H, d, J=4.2 Hz), 3.5(2H, m), 3.77(3H, s), 5.15(1H, d, J=4.8 Hz), 5.27(2H, s), 5.59, 6.14(2H, ABq, J=15.0 Hz), 5.82(2H, d, J=56.0 Hz), 5.96(1H, m), 6.93(2H, d, J=8.4 Hz), 7.37(2H, d, J=8.4 Hz), 7.96(1H, dd, J=9.0 Hz, 5.6 Hz), 8.37(1H, d, J=5.6 Hz), 8.87(1H, d, J=9.0 Hz), 8.90(1H, d. J=8.2 Hz),9.01(1H, s), 12.67(1H, s)

IR(Nujol)cm^{-1}: 1780,1705,1660,1455,1370

(2) Compound 41c (2.38 g, 2.5 mmol) was dissolved in CH_2Cl_2 50 ml and $MeNO_2$ 25 ml and the mixture was ice-cooled. Anisole (3.26 ml, 12eq) and $TiCl_4$ (2.75 ml, 10eq) were added thereto and the mixture was stirred at 5°C for 1 hr. The reaction mixture was poured into 0.25N HCl 200 ml and Et_2O 300 ml中 with stirring. The water layer was separated, washed with Et_2O 300 ml and purified with HP-20SS chromato. The eluted portion was lyophilized to give compound 42c (0.60 g, 36%).

^{1}H-NMR(D_2O) δ : 2.81(3H, s), 3.26, 3.61(2H, ABq, J=18.1 Hz), 5.213(1H, d, J=4.8 Hz), 5.33(2H, s), 5.67, 5.91(2H, ABq, J=14.8 Hz), 5.82(2H, d, J=53.4 Hz), 5.85(1H, d, J=4.8 Hz), 7.87(1H, dd, J=8.2 Hz, 5.8 Hz), 8.65(1H, d, J=8.2 Hz), 8.82(1H. s), 8.90(1H, d, J=5.8 Hz)

IR(KBr)cm^{-1}: 1774,1675,1613,1527,1387

Elementary Analysis as $C_{22}H_{21}N_{10}O_6S_2F \cdot 3.2H_2O$

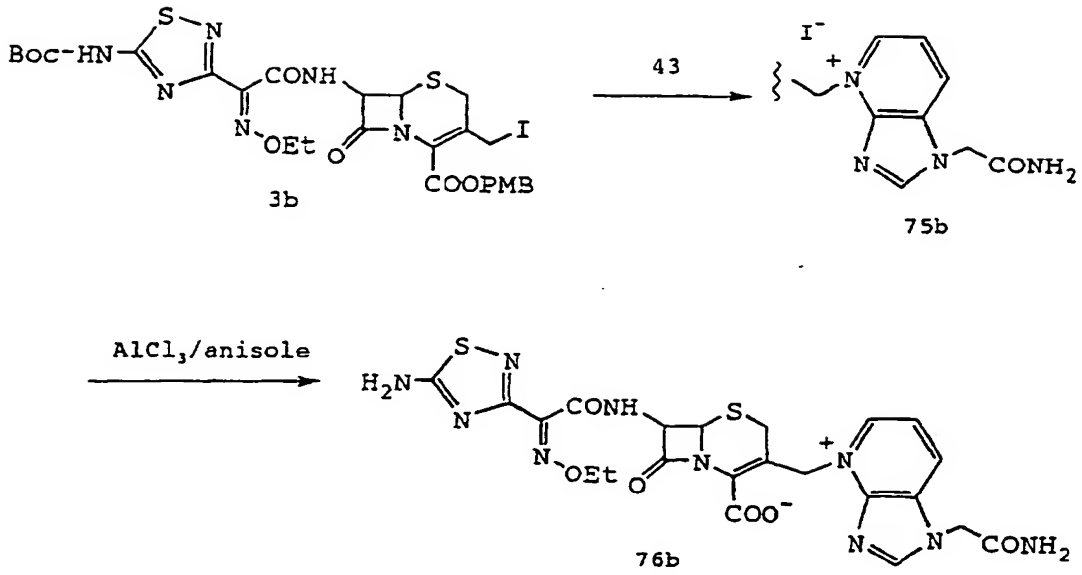
calc. : C,39.90; H,4.17; N,21.15; S,9.68; F,2.87

found: C,39.91; H,4.25; N,21.32; S,9.84; F,2.68

[0193] The compounds of Examples 10 to 33 shown below were synthesized by using materials obtained in Reference Examples 13 to 33.

Example 10

[0194]



(1) To a solution of compound 43 (0.264 g, 1.5 mmol) of Reference Example 13 in DMF 7 ml, was dissolved a solution of compound 3b (1.48 g, 1.3eq) in MeCN 4 ml under stirring and ice-cooling and the mixture was stirred at room temperature for 1.5 hr. From the reaction mixture, MeCN was evaporated under reduced pressure and the residue was slowly added to Et_2O 400 ml under stirring. The precipitate was filtered to give compound 75b (1.41 g, yield 100%).

^{1}H-NMR(DMSO-d6) δ :1.24(3H,t,J=7.2Hz), 1.51(9H,S), 3.77(3H,S), 4.20(2H,q,J=7.2Hz), 5.13(1H,d,J=5Hz), 5.28(2H,m), 5.58,6.14(2H,ABq,J=14.6Hz), 5.93(1H,dd,J=8.6Hz, 5Hz), 6.93(2H,d,J=8.8Hz), 7.34(2H,d,J=8.8Hz), 7,57(1H,S), 7.88(1H,S), 7.96(2H,m), 8.88(1H,m), 9.01(1H,S), 9.68(1H,d,J=8.6Hz), 12.59(1H,S)

IR($CHCl_3$)cm^{-1}:3250,1780,1710,1680,1550,1390

(2) Compound 75b (1.40 g, 1.5 mmol) was dissolved in CH_2Cl_2 30 ml and $MeNO_2$ 10 ml and the mixture was cooled to -20°C with stirring. Anisole (1.95 ml, 12eq) and an $AlCl_3$-$MeNO_2$ solution (1M, 15ml, 10eq.) were added thereto and the mixture was stirred at -5°C for 30 min. The reaction mixture was poured into 0.25N HCl 70 ml and Et_2O 140 ml with stirring. The water layer was separated, washed with Et_2O 140 ml, and purified with HP-20. The eluted portion was lyophilized to give compound 76b (0.42 g, yield 43%).

^{1}H-NMR(D_2O) δ :1.29(3H,t,J=7Hz), 3.28,3.61(2H,ABq.J=18Hz), 4.31(2H,q,J=7Hz), 5.22(1H,d,J=4.6Hz), 5.40(2H,S), 5.66,5.91(2H,ABq,J=14.6Hz), 5.86(1H,d,J=4.6Hz), 7.83(1H,dd,J=6.2Hz,8.4Hz), 8.69(1H,d,J=8.4Hz), 8.83(1H,S), 8.90(1H,d,J=6.2Hz)

IR(KBr)cm^{-1}:1770,1684,1613,1525

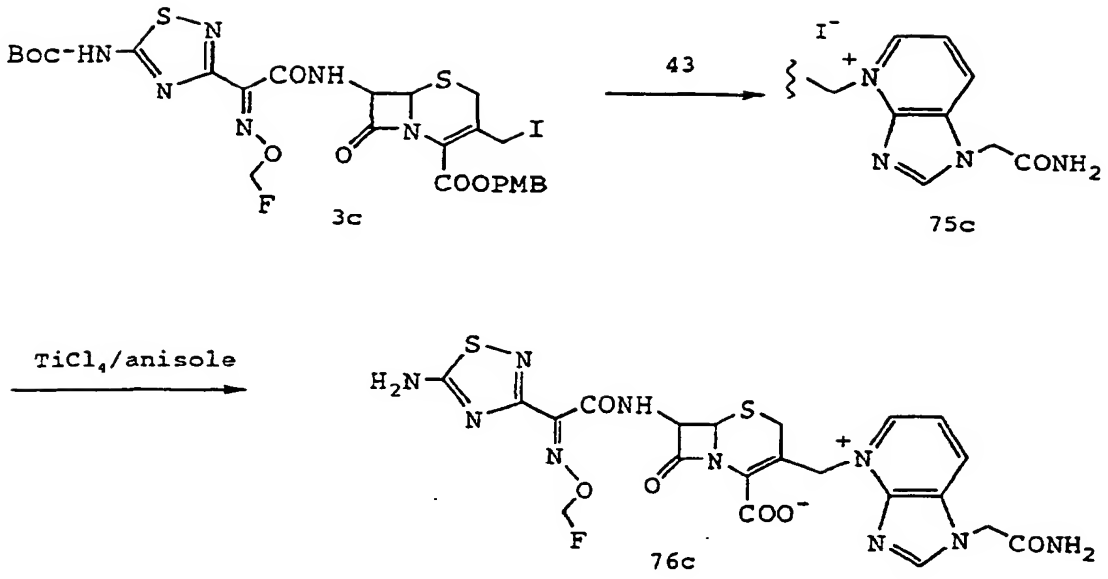
Elementary Analysis as $C_{22}H_{22}N_{10}O_6S_2 \cdot 3.5H_2O$

calc. : C,40.67; H,4.50; N,21.56; S,9.87

found: C,40.66; H,4.18; N,21.39; S,9.92

Example 11

[0195]



(1) To a solution of compound 43 (0.529 g, 3 mmol) of Reference Example 13 in DMF 14 ml, was added a solution of compound 3c (2.38 g, 1.2eq) in MeCN 3 ml under stirring and ice-cooling and the mixture was stirred at room temperature for 2 hr. From the reaction mixture, MeCN was evaporated under reduced pressure and the residue was slowly added to Et_2O 600 ml. The precipitate was filtered to give compound 75c (2.64 g, yield 100%).

^{1}H-NMR(DMSO-d6) δ :151(9H,S), 3.77(3H,S), 5.15(1H,d,J=5Hz), 5.26(2H,m), 5.59,6.12(2H,ABq,J=14.5Hz), 5.82 (2H,d,J=56.4Hz), 6.93(2H,d,J=8.6Hz), 7.57(1H,S), 7.93(3H,m), 7.37(2H,d,J=8.6Hz), 8.88(1H,m). 9.01(1H,S), 9.89 (1H,d,J=8.6Hz), 12.66(1H,S)

IR($CHCl_3$)cm^{-1}:1775,1715,1670,1545,1385

(2) Compound 75c (2.63 g, 3.14 mmol) was dissolved in CH_2Cl_2 60 ml and $MeNO_2$ 30 ml and the mixture was cooled under stirring. Anisole (4.09 ml, 12eq) and $TiCl_4$ (3.45 ml, 10eq) were added thereto and the mixture was stirred at 5°C for 1.5 hr. The reaction mixture was poured into a mixture of 0.25N HCl 200 ml and Et_2O 280 ml with stirring. The water layer was separated, washed with Et_2O 280 ml, and purified with HP-20. The eluted portion was lyophilized to give compound 76c (0.50 g, yield 25%).

^{1}H-NMR(D_2O)δ :3.26,3.61(2H,ABq,J=18.0Hz), 5.23(2H,d,J=5Hz), 5.39(2H,S), 5.65,5.90(2H,ABq,J=14.0Hz), 5.81 (2H,d,J=53.6Hz), 5.86(1H,d,J=5Hz), 7.87(1H,dd,J=8.4Hz,6.2Hz), 8.68(1H,d,J=8.4Hz), 8.82(1H,S), 8.90(1H,d, J=6.2Hz)

IR(KBr)cm^{-1}:1770,1684,1614,1525,1487,1463

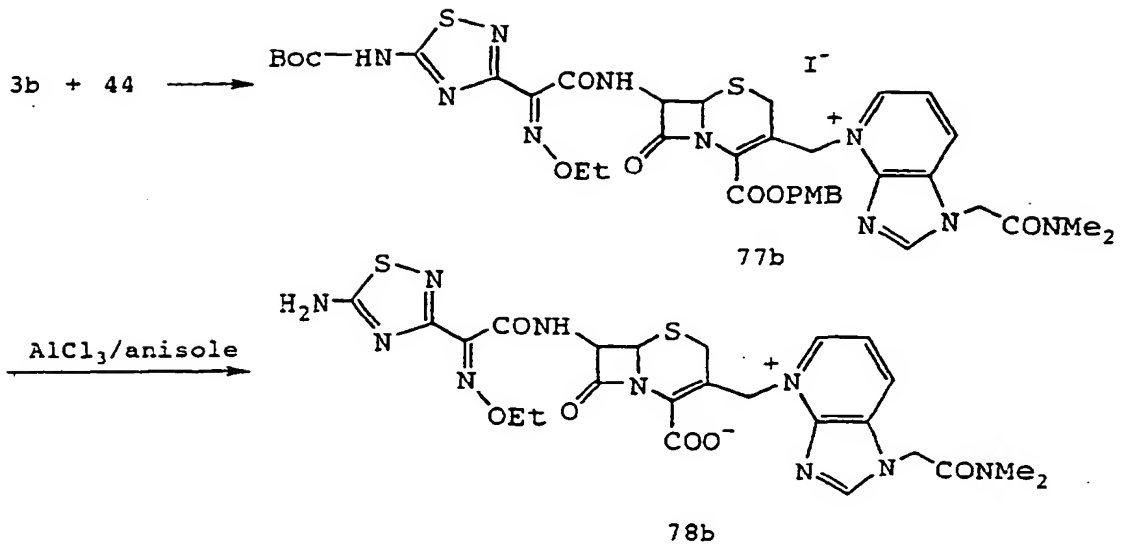
Elementary Analysis as $C_{21}H_{19}N_{10}O_6S_2F\cdot3.6H_2O$

calc. : C,38.48; H,4.03; N,21.37; S,9.78; F,2.90

found: C,38.46; H,3.73; N,21.16; S,9.55; F,2.74

Example 12

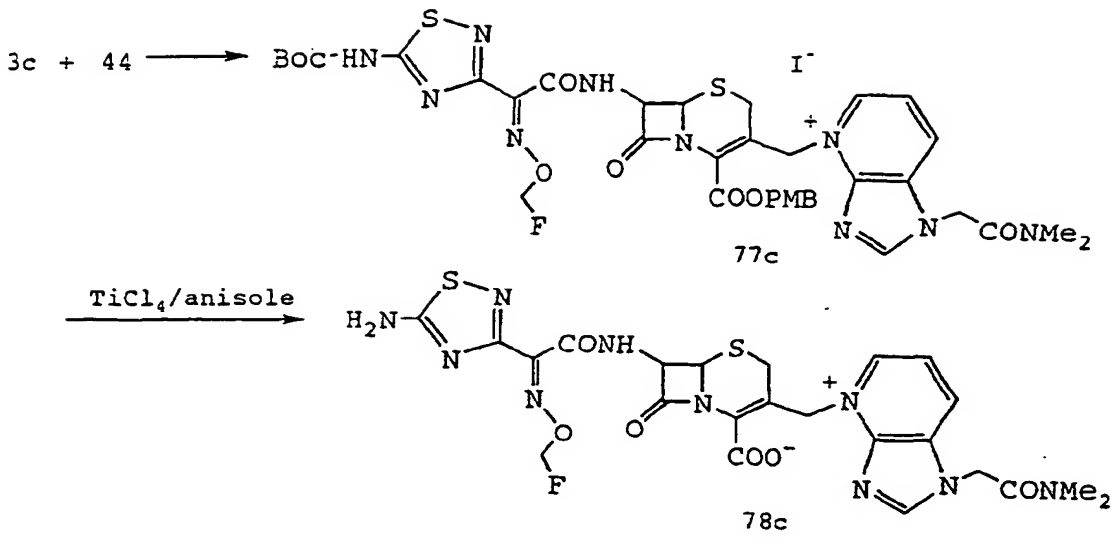
[0196]



(1) Compound 44 (0.245 g, 1.2 mmol) of Reference Example 14 and compound 3b (1.18 g, 1.3eq) were dissolved into DMF 8 ml and the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was slowly added to Et_2O 300 ml, then the precipitate was filtered to give compound 77b (1.26 g, yield 100%).
^{1}H-NMR(DMSO-d6) δ :1.24(3H,t,J=7Hz), 1.51(9H,S), 2.91(3H,S), 3.14(3H,S), 3.77(3H,S), 4.20(2H,q,J=7Hz), 5.14(1H,d,J=5Hz), 5.25,5.31(2H,ABq,J=12.2Hz), 5.59(4H,m), 5.93(1H,dd,J=5Hz), 5.93(2H,d,J=8.4Hz), 7.37(2H,d,J=8.4Hz), 7.95(2H,m), 8.89(1H,m), 8.93(1H,S), 9.68(1H,d,J=8.2Hz), 12.59(1H,S)
IR(Nujol)cm^{-1}:1785,1715,1660,1545,1460,1379
(2) Compound 77b (1.24 g, 1.29 mmol) was dissolved into CH_2Cl_2 26 ml and CH_3NO_2 8 ml and the mixture was cooled to -20°C under stirring. Anisole (1.68 ml, 12eq) and an $AlCl_3$/$MeNO_2$ solution(1M, 12.9ml, 10eq) were added thereto and the mixture was stirred at -5 °C for 30 min. The reaction mixture was poured into a mixture of .25N HCl 70 ml and Et_2O 140 ml with stirring. The water layer was separated, washed with Et_2O 140 ml, and purified with HP-20. Lyophilization gave compound 78b (0.37 g, yield 45%).
^{1}H-NMR(D_2O) δ :1.29(3H,t,J=7Hz), 2.30(3H,S), 3.21(3H,S), 3.27,3.61(2H,ABq,J=19.6Hz), 4.31(2H,q,J=7Hz), 5.22(1H,d,J=5Hz), 5.58(2H,S), 5.66,5.90(2H,ABq,J=14.8Hz), 5.86(1H,d,J=5Hz), 7.87(1H,dd,J=8.2Hz,6Hz), 8.61(1H,d,J=8.2Hz), 8.76(1H,S), 8.89(1H,d,J=6Hz)
IR(KBr)cm^{-1}:1774,1654,1524,1463,1384
Elementary Analysis as $C_{24}H_{26}N_{10}O_6S_2$·4.2H_2O
calc. : C,41.76; H,5.02; N,20.29; S,9.29
found: C,41.83; H,4.94; N,20.47; S,9.47

Example 13

[0197]



(1) Compound 44 (0.408 g, 2 mmol)of Reference Example 14 and compound 3c (1.83 g, 1.2eq) were dissolved in DMF 13 ml and the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was slowly added to Et_2O 500 ml, then the precipitate was filtered to give compound 77c (2.05 g, yield 100%).

^{1}H-NMR(DMSO-d6) δ :1.52(9H,S), 2.91(3H,S), 3.15(3H,S), 3.77(3H,S), 5.16(1H,d,J=4.8Hz), 5.30(2H,m), 6.00 (2H,m), 5.8(2H,d,J=55Hz), 6.93(2H,d,J=8.6Hz), 7.37(2H,d,J=8.6Hz), 7.96(2H,m), 8.87(1H,m), 8.93(1H,S), 12.67 (1H,S)

IR(Nujol)cm^{-1}:1785,1710,1660,1460,1379

(2) Compound 77c (2.03 g, 2 mmol) was dissolved in CH_2Cl_2 40 ml and $MeNO_2$ 20 ml and the mixture was cooled under stirring. Anisole (2.61 ml, 12eq) and $TiCl_4$ (2.20 ml, 10eq) were added thereto and the mixture was stirred at 5°C for 1.5 hr. The reaction mixture was poured into a mixture of 0.25N HCl 200 ml and Et_2O 300 ml with stirring. The water layer was separated, washed with Et_2O 300 ml, and purified with HP-20. Lyophilization gave compound 78c (0.27 g, yield 20%).

^{1}H-NMR(D_2O) δ :3.0(3H,S), 3.21(3H,S), 3.26,3.61(2H,ABq,J=18.1Hz), 5.23(1H,d,J=4.8Hz), 5.58(2H,S), 5.81(2H, d,J=54.2Hz), 5.66,5.90(2H,ABq,J=14.8Hz), 5.86(1H,d,J=4.8Hz), 7.86(1H,dd,J=8.2Hz,6.2Hz), 8.60(1H,d, J=8.2Hz), 8.76(1H,S), 8.89(1H,d,J=6.2Hz)

IR(KBr)cm^{-1}:1773,1651,1527,1491,1463,1394

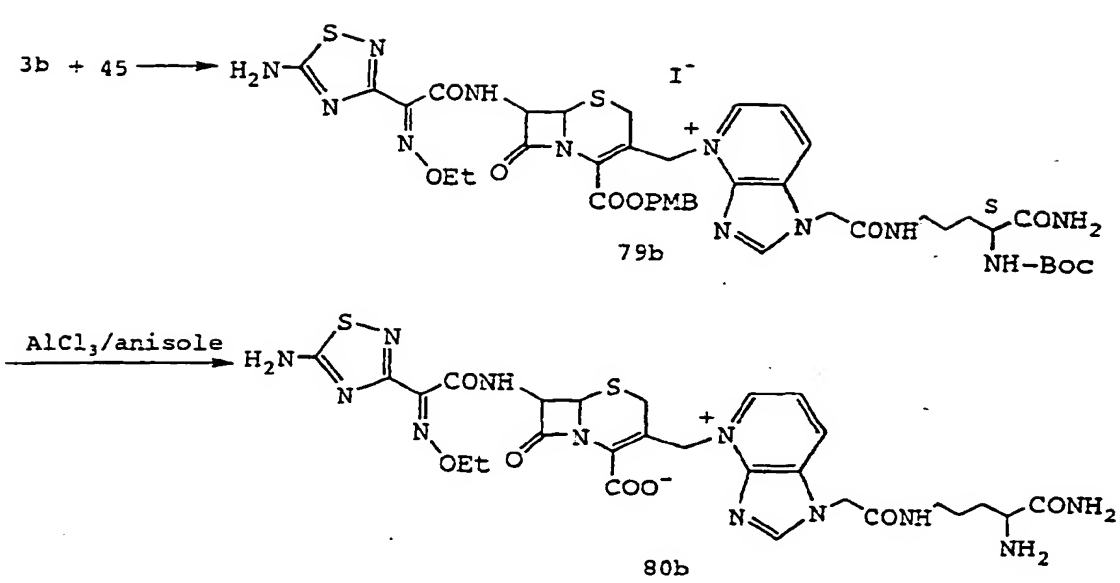
Elementary Analysis as $C_{23}H_{23}N_{10}O_6S_2F\cdot4.1H_2O$

calc. : C,39.89; H,4.54; N,20.23; S,9.26; F,2.74

found: C,39.93; H,4.58; N,20.40; S,9.34; F,2.68

Example 14

[0198]



(1) Compound 45 (0.507 g, 1.3 mmol) of Reference Example 15 and compound 3b (1.28 g, 1.3eq) were dissolved in DMF 8 ml and the mixture was stirred at 3°C for 16 hr. The reaction mixture was added to 300ml of Et_2O under stirring, then the precipitate was filtered to give compound 79b (1.16 g, yield 78%).

^{1}H-NMR(DMSO-d6)δ:125(3H,t,J=7Hz), 1.40(9H,S), 1.51(9H,S), 3.78(3H,S), 4.22(2H,q,t=7Hz), 5.15(1H,q, J=5Hz), 5.60,6.15(2H.ABq,J=14.2Hz), 5.95(1H,dd,J=9Hz,5Hz), 6.94(2H,d,J=8.6Hz), 7.38(2H,d,J=8.6Hz), 7.95 (1H,m), 8.88(1H,m), 9.02(1H,S), 9.68(1H,(1,J=9Hz), 12.6(1H,S)

IR($CHCl_3$)cm^{-1}: 1780,1715,1680,1545,1515

(2) Compound 79b (1.16 g, 1.01 mmol) was dissolved in CH_2Cl_2 20 ml and $MeNO_2$ 7 ml and the mixture was stirred under cooling. Anisole (1.32 ml, 12eq) and an $AlCl_3/MeNO_2$ solution (1M, 10.1ml,10eq.) were added thereto and the mixture was stirred at 5°C for 1.5 hr. The reaction mixture was poured into a mixture of 0.25N HCl 50 ml and Et_2O 100 ml with stirring. The water layer was separated, washed with Et_2O 100 ml, and purified with HP-20. Lyophilization gave compound 80b (0.12 g, yield 15%).

^{1}H-NMR(D_2O) δ : 1.27(3H,t,J=7Hz), 4.30(2H,d,J=7Hz), 5.20(1H,d,J=4.6Hz), 5.33(2H,S), 5.63,5.89(2H,ABq, J=14.6Hz), 5.84(1H,d,J=4.6Hz), 7.86(1H,dd,J=8.2Hz,6.6Hz), 8.64(1H,d,J=8.2Hz), 8.80(1H,S), 8.88(1H,d, J=6.6Hz)

IR(KBr)cm^{-1}:1772,1671,1612,1526,1462,1385

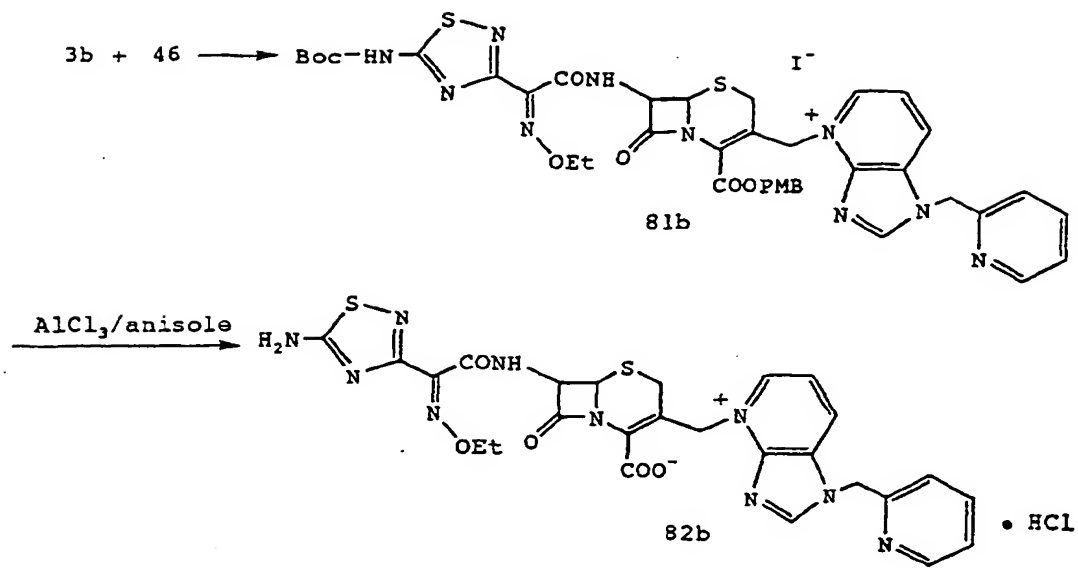
Elementary Analysis as $C_{27}H_{32}N_{12}O_7S_2 \cdot 4.6H_2O$

calc. : C,41.92; H,4.07; N,21.73; S,8.29

found: C,41.41; H, 5.09; N,21.26; S,8.47

Example 15

[0199]



(1) Compound 46 (0.318 g, 1.51 mmol) of Reference Example 16 and compound 3b (1.38 g, 1.2eq) were dissolved in DMF 7 ml and the mixture was stirred at room temperature for 45 min. The reaction mixture was added to Et_2O 300 ml under stirring, then the precipitate was filtered to give compound 81b (1.48 g, yield 100%).

^{1}H-NMR(DMSO-d6) δ :1.24(3H,t,J=7,2Hz), 1.51(9H,S), 3.76(3H,S), 4.20(2H,q,J=7.2Hz), 5.11(1H,d,J=5Hz), 5.29 (2H,m), 5.60,6.14(2H,ABq,J=18.6Hz), 6.0(3H,m), 6.93(2H,d,J=8.6Hz), 7.38(2H,d,J=8.6Hz), 7.60(1H,d,J=7,2Hz), 7.89(4H,m), 8.50(1H,m), 8.9(2H,m), 9.19(1H,S), 9.67(1H,d,J=8.2Hz), 12.59(1H,S)

IR(Nujol)cm^{-1}:1790,1715,1675,1550,1461,1380

(2) Compound 81b (1.46 g, 1.5 mmol) was dissolved in CH_2Cl_2 30 ml and $MeNO_2$ 10 ml under stirring and cooling. Anisole 1.97 ml (12eq) and an $AlCl_3/MeNO_2$ solution (1M, 15 ml, 10eq) were added thereto and the mixture was stirred at 5°C for 1.5 hr. The reaction mixture was poured into 0.25N HCl 70 ml and Et_2O 140 ml with stirring. The water layer was separated, washed with Et_2O 140 ml, and purified with HP-20. Lyophilization gave compound 82b (0.40 g, yield 38%).

^{1}H-NMR(D_2O) δ :1.30(3H,t,J=7.4Hz), 3.32,3.64(2H,ABq,J=18.2Hz), 4.32(2H,q,J=7.4Hz), 5.24(1H,d,J=5Hz), 5.69,5.94(2H,ABq,J=14.6Hz), 5.86(1H,d,J=5Hz), 5.95(2H,S), 7.59(2H,m), 7.82(1H,dd,J=8.2Hz,6.2Hz), 8.06(1H, m), 8.52(1H,m), 8.55(1H,d,J=8,2Hz), 8.89(1H,d,J=6.2Hz), 8.98(1H,S),

IR(KBr)cm^{-1}:1776,1672,1617,1525,1483,1461,1438

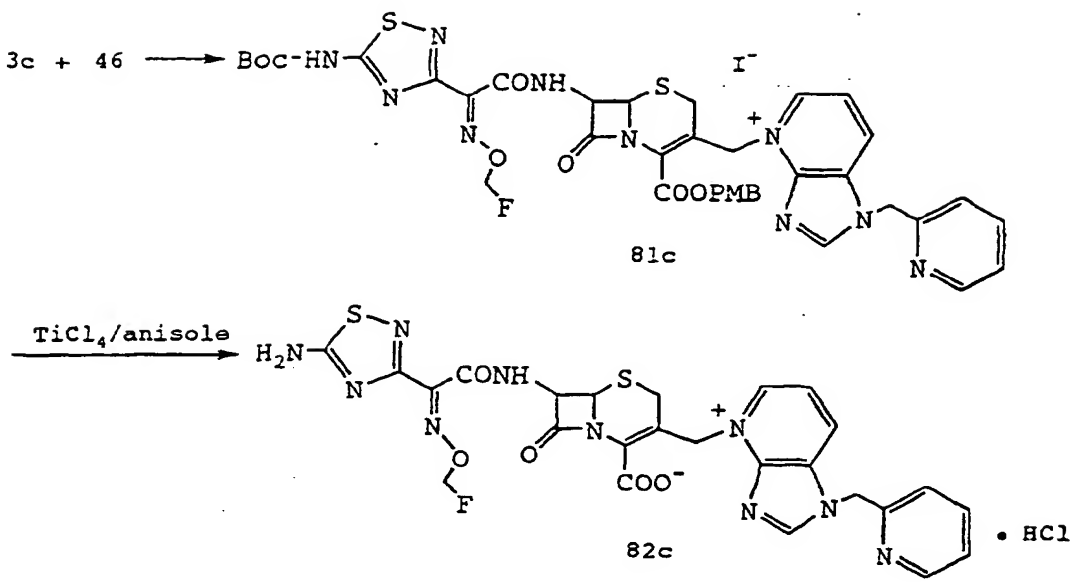
Elementary Analysis as $C_{26}H_{24}N_{10}O_5S_2 \cdot 0.3HCl, 3.6H_2O$

calc. : C,44.84; H,4.56; N,20.11; S,9.21; Cl,1.53

found: C,44.80; H,4.58; N,20.13; S,9.05; Cl,1.69

Example 16

[0200]



(1) To a solution of compound 46 (0.42 g, 2 mmol) of Reference Example 16 and compound 3c (1.83 g, 1.2eq) in DMF 8 ml and the mixture was stirred at room temperature for 1 hr. The reaction mixture was added to Et_2O 300 ml under stirring, then the precipitate was filtered to give compound 81c (2.12 g, yield 100%).

^{1}H-NMR(DMSO-d6) δ :1.51(9H,S), 3.76(3H,S), 5.13(1H,d,J=5.2Hz), 5.28(2H,m), 5.66(3H,m), 5.92(3H,m), 6.92 (2H,d,J=8.4Hz), 7.37(2H,d,J=8.4Hz), 7.60(1H,d,J=7.8Hz), 7.93(2H,m), 8.49(1H,m), 8.84(1H,d,J=6.8Hz), 8.94(1H, d,J=8.2Hz), 9.20(1H,S), 12.7(1H,S)

IR(Nujol)cm^{-1}:1785,1710,1655,1540,1459,1375

(2) Compound 81c (2.11 g, 2.17 mmol) was dissolved in CH_2Cl_2 40 ml and $MeNO_2$ 20 ml under stirring and cooling. Anisole (2.83 ml, 12eq) and $TiCl_4$ (2.38 ml, 10eq) were added thereto and the mixture was stirred at 5°C for 1.5 hr. The reaction mixture was poured into 0.25N HCl 120 ml and Et_2O 250ml with stirring. The water layer was separated, washed with Et_2O 250 ml, and purified with HP-20. Lyophilization gave compound 82c (0.34 g, yield 22%).

^{1}H-NMR(D_2O) δ :3:31,3.64(2H,ABq,J=17.4Hz), 5.24(1H,d,J=5Hz), 5.69,5.94(2H,ABq,J=14.6Hz), 5.88(1H,d, J=5Hz), 5.83(2H,d,J=58Hz), 5.97(1H,S), 7.62(2H,m), 7.80(1H,dd,J=8.2Hz,6.2Hz), 8.11(1H,m), 8.54(2H,m), 8.88 (1H,d,J=6.2Hz), 8.97(1H,S)

IR(KBr)cm^{-1}:1775,1676,1616,1525,1484,1462,1438

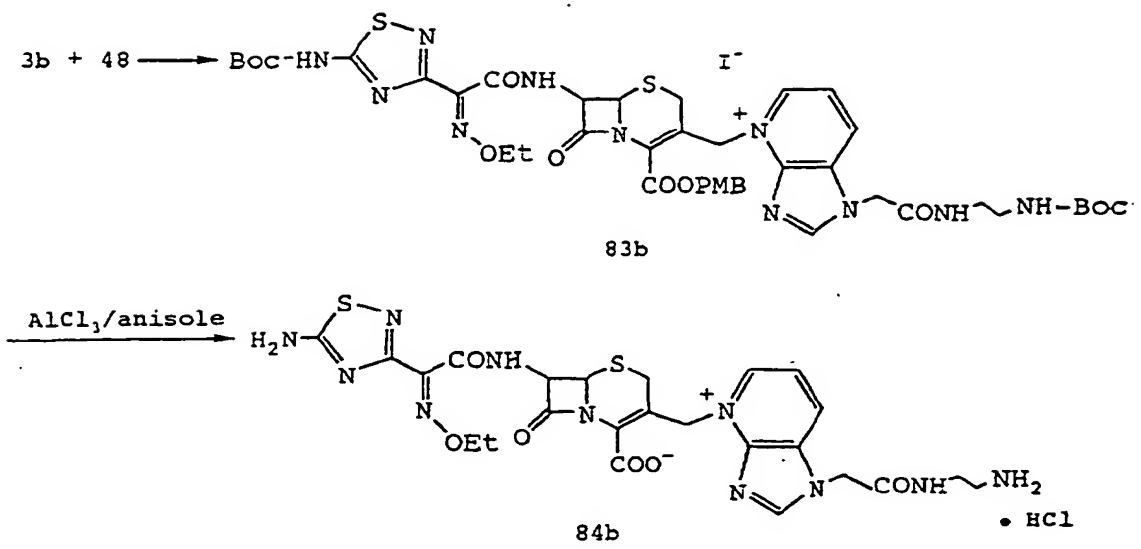
Elementary Analysis as $C_{25}H_{21}N_{10}O_5S_2F\cdot0.6HCl,3.6H_2O$

calc. : C,42.21; H,4.08; N,19.69; S,9.01; F,2.67; Cl,2.99

found: C,42.29; H,4.13; N,19.63; S,8.79; F,2.62; Cl,2.95

Example 17

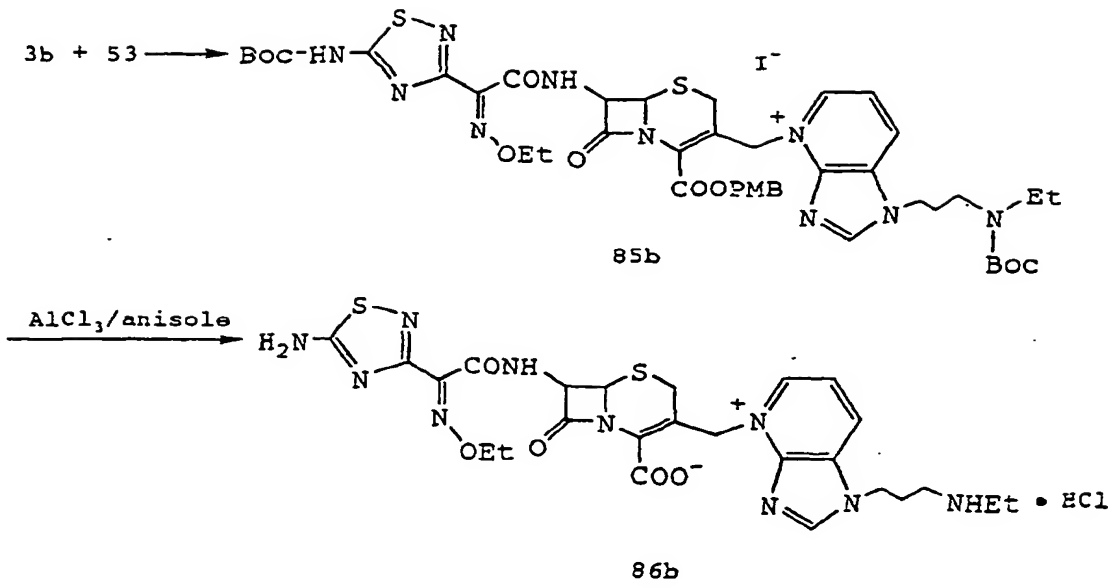
[0201]



(1) Compound 48 (0.45 g, 1.71 mmol) of Reference Example 17 and compound 3b (1.69 g, 1.3eq) of Example 10 were dissolved in DMF 7 ml and the mixture was stirred at room temperature for 1hr. The reaction mixture was added to Et_2O 300 ml under stirring, then the precipitate was filtered to give compound 83b (2.03 g, yield 100%).
^{1}H-NMR(DMSO-d6) δ :1.22(9H,S), 1.23(3H,t,J=7Hz), 1.50(9H,S), 3.77(3H,S), 4.19(2H,q,J=7Hz), 4.52(2H,m), 5.09(1H,d,J=5.2Hz), 5.29(2H,m), 5.62,6.09(2H,ABq,J=14.6Hz), 5.94(1H,dd,J=8.2Hz,5.2Hz), 6.95(2H,d,J=9Hz), 7.39(2H,d,J=9Hz). 7.98(1H,m), 8.88(1H,d,J=6.2Hz), 8.96(1H,d,J=8.2Hz), 9.01(1H,S), 9.65(1H,d,J=8.2Hz), 12.59 (1H,S)
IR($CHCl_3$)cm^{-1}:1780,1720,1695,1545,1518,1390
(2) Compound 83b (1.83 g, 1.79 mmol) was dissolved in CH_2Cl_2 36 ml and $MeNO_2$ 12 ml and the mixture was stirred under cooling. Anisole (2.34 ml, 12eq) and 1mol $AlCl_3/MeNO_2$ (17.9ml, 10eq.) was added thereto under stirring at 5°C for 1.5 hr. The reaction mixture was poured into a mixture of 0.25N HCl 80 ml and Et_2O 160 ml with stirring. The water layer was separated, washed with Et_2O 160 ml, and purified with HP-20. Lyophilization gave compound 84b (0.44 g, yield 35%).
^{1}H-NMR(D_2O) δ :1.31(3H,t,J=7.2Hz), 3.32,3.63(2H,ABq,J=17.7Hz), 3.67(3H,m), 4.33(2H,q,J=7.2Hz), 4.91(2H,t, J=6Hz), 5.22(1H,d,J=5Hz), 5.64,5.94(2H,ABq,J=14.8Hz), 5.85(1H,d,J=5Hz), 7.92(1H,dd,J=8.2Hz,6.4Hz), 8.86 (1H,d,J=8.2Hz), 8.87(1H,d,J=6.4Hz), 8.92(1H,S)
IR(KBr)cm^{-1}:1772,1669,1634,1524,1488,1464
Elementary Analysis as $C_{22}H_{24}N_{10}O_5S_2 \cdot 1.4HCl, 3.9H_2O$
calc. : C,38.08; H,4.82; N,20.18; S,9,24; Cl,7.15
found: C,38.04; H,4.96; N,19.80; S,9.09; Cl,7.11

Example 18

[0202]



(1) To a solution of compound 53 (0.59 g, 1.94 mmol) of Reference Example 19 in MeCN 5ml, was added a solution of compound 3b (1.62 g, 1.1eq) in MeCN 10 ml under ice-cooling and the mixture was stirred at room temperature for 1.5 hr. From the reaction mixture was evaporated MeCN, then Et_2O 70 ml was added to the reside, then the precipitate was filtered to give compound 85b (1.69 g, yield 82%).

^{1}H-NMR(DMSO-d6) δ :1.05(3H,m), 1.23(3H,t,J=6.6Hz), 1.35(9H,S), 1.51(9H,S), 2.1(2H,m), 3.19(4H,m), 3.76(3H,S), 4.20(2H,q,J=7.2Hz), 4.45(2H,m), 5.1(1H,d,J=4.8Hz), 5.27,5.31(2H,ABq,J=12.3Hz), 5.96(1H,dd,J=8.7Hz, 4.8Hz), 5.59,6.11(2H,ABq,J=147Hz), 6.93(2H,d,J=8.7Hz), 7.38(2H,d,J=8.7Hz), 7.96(1H,m), 8.86(1H,d,J=6.3Hz), 9.03(1H,d,J=8.1Hz), 9.11(1H,S), 9.68(1H,d,J=8.7Hz), 12.59(1H,S)

IR(Nujol)cm^{-1}:1780,1715,1680,1545,1460,1380

(2) Compound 85b (1.67 g, 1.57 mmol) was dissolved in CH_2Cl_2 30 ml and $MeNO_2$ 8 ml and the mixture was stirred under cooling. Anisole (2.05 ml, 12eq) and 1mol $AlCl_3/MeNO_2$ (15.7 ml, 10eq) were added thereto and the mixture was stirred at 5°C for 1.5 hr. The reaction mixture was poured in a mixture of 0.25N HCl 40 ml and Et_2O 80 ml with stirring. The water layer was separated, washed with Et_2O 80 ml, and purified with HP-20. Lyophilization gave compound 86b (0.40 g, yield 33%).

^{1}H-NMR(D_2O) δ :1.29(6H,m), 2.40(2H,m), 312(4H,m), 3.34,3.65(2H,ABq,J=18.4Hz), 4.33(2H,q,J=7.2Hz), 4.64 (2H,t,J=7Hz), 5.25(1H,d,J=4.6Hz), 5.70,5.94(2H,ABq,J=14.8Hz), 5.88(1H,d,J=4.6Hz), 7.89(1H,dd,J=8.2Hz, 6.4Hz), 8.81(1H,d,J=8.2Hz), 8.85(1H,d,J=6.4Hz), 8.89(1H,S)

IR(KBr)cm^{-1}:1779,1671,1633,1526,1488,1463

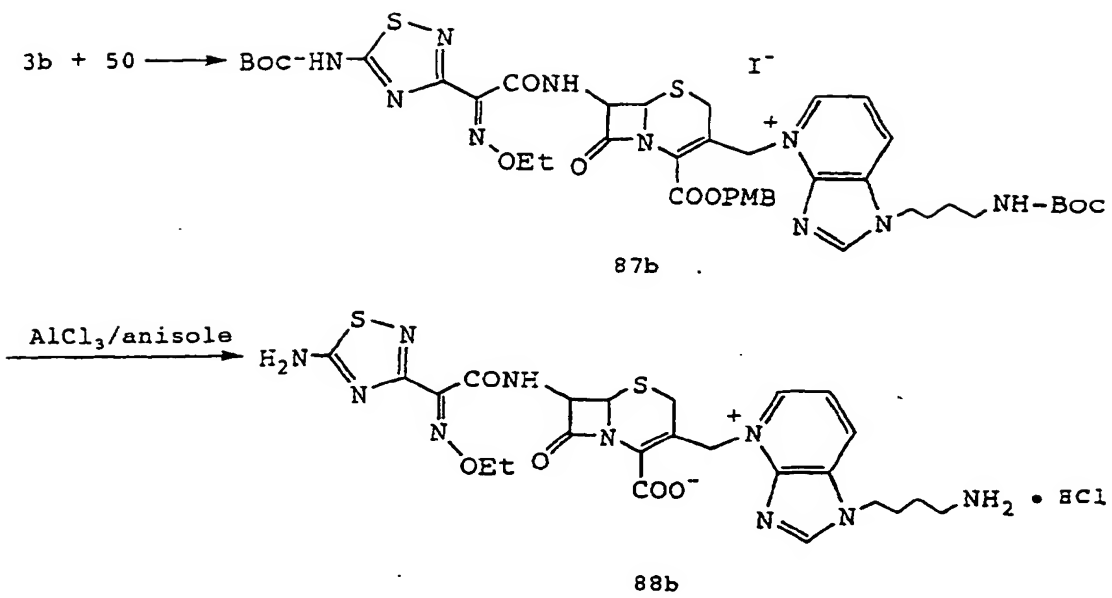
Elementary Analysis as : $C_{25}H_{30}N_{10}O_5S_2 \cdot 1.8HCl,4.7H_2O$

calc. C,39.24; H,5.44; N,18.31; S,8.38; Cl,8.34

found C,39.25; H,5.20; N,18.30; S,8.43; Cl,8.53

Example 19

[0203]



(1) Compound 50 (0.44 g, 1.52 mmol) of Reference Example 18 and compound 3b (1.38 g, 1.2eq) were dissolved in DMF 7 ml and the mixture was stirred at room temperature for 1hr. The reaction mixture was added to Et_2O 300 ml under stirring, then the precipitate was filtered to give compound 87b (1.51 g, yield 95%).

^{1}H-NMR(DMSO-d6) δ :1.23(3H,t,J=7.5Hz), 1.36(9H,S), 1.51(9H,S), 1.85(2H,m), 2.9.5(2H,m), 3.77(3H,S), 4.20 (2H,q,J=7.5Hz), 4.50(2H,m), 5.10(1H,d,J=4.5Hz), 5.27,5.30(2H,ABq,J=12.0Hz). 5.57,6.10(2H,ABq,J=14.6Hz), 5.95(1H,dd,J=8.4Hz,4.5Hz), 6.93(2H,d,J=8.7Hz), 7.38(2H,d,J=8.7Hz), 7.96(1H,m), 8.85(1H,d,J=6Hz), 9.03(1H,d, J=8.4Hz), 9.07(1H,S),9.66(1H,d,J=8.4Hz), 12.6(1H,S)

IR(Nujol)cm^{-1}:1790,1710,1690,1545,1515,1460,1380

(2) Compound 87b (1.49 g, 1.42 mmol) was dissolved in CH_2Cl_2 30 ml and $MeNO_2$ 10 ml and the mixture was stirred under cooling. Anisole (1.85 ml, 10eq) and 1mol $AlCl_3/MeNO_2$ (14.2 ml, 10eq) were added thereto and the mixture was stirred at 5°C for 1.5 hr. The reaction mixture was poured into a mixture of 0.25N HCl 60 ml and Et_2O 120 ml with stirring. The water layer was separated, washed with Et_2O 120 ml, and purified with HP-20. Lyophilization gave compound 88b (0.28 g, yield 27%).

^{1}H-NMR(D_2O) δ :1.30(3H,t,J=7Hz), 1.75(2H,m), 2.05(2H,m), 3.04(2H,t,J=6.8Hz), 3.31,3.64(2H,ABq,J=18.1Hz), 4.33(2H,q,J=7Hz), 4.57(2H,t,J=7Hz), 5.23(1H,d,J=5Hz), 5.64,5.89(2H,ABq,J=14.8Hz), 5.85(1H,d,J=5Hz), 7.86 (1H,dd,J=8.2Hz,6.6Hz), 8.78(1H,d,J=8.2Hz), 8.81(1H,d,J=6.6Hz), 8.85(1H,S)

IR(KBr)cm^{-1}:1774,1671,1617,1523,1489,1462

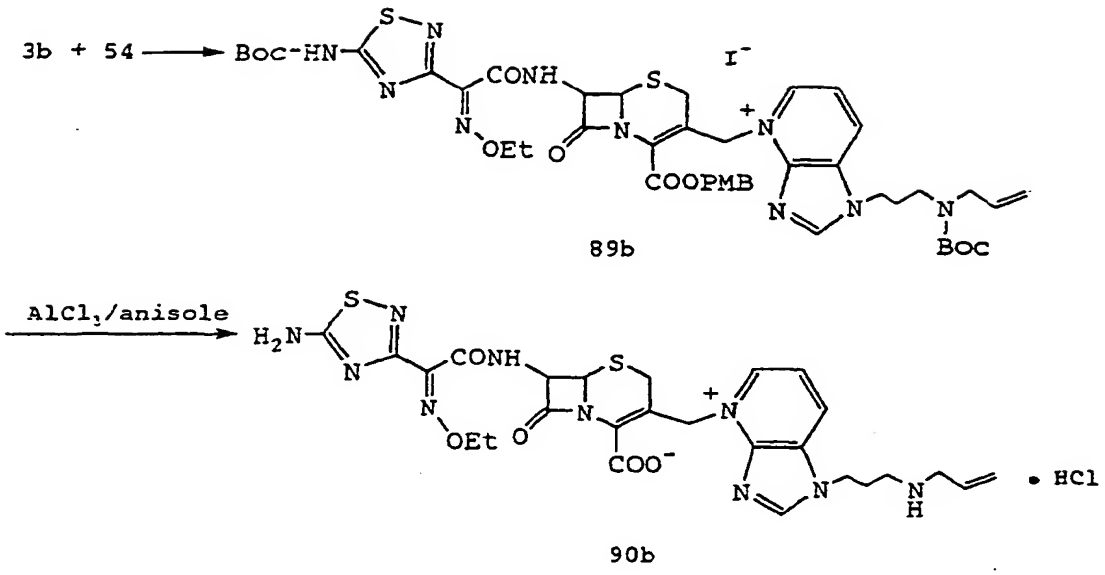
Elementary Analysis as $C_{24}H_{28}N_{10}O_5S_2 \cdot 1.6HCl, 4.3H_2O$

calc. : C,39.14; H,5.23; N,19.02; S,8.71; Cl,7.70

found: C,39.23; H,5.17; N,19.13; S,8.57; Cl,7.68

Example 20

[0204]



(1) To a solution of compound 54 (0.41 g, 1.3 mmol) of Reference Example 20 in MeCN 4 ml, was added a solution of compound 3b (1.08 g, 1.1eq) in MeCN 8 ml under stirring and ice-cooling and the mixture was stirred at room temperature for 1.5 hr. From the reaction mixture, MeCN was evaporated under reduced pressure and the residue was washed with Et_2O 60 ml to give compound 89b (1.33 g, yield 95%).

^{1}H-NMR(DMSO-d6)δ:1.23(3H,t,J=7.2Hz), .35(9H,S), 1.51(9H,S), 2.10(2H,m), 3.20(2H,m), 3.77(3H,S), 4.19(2H, q,J=7.2Hz), 4.45(2H,m), 5.11(3H,m), 5.29(1H,d,J=4.2Hz), 5.59,6.10(2H,ABq,J=14.7Hz), 5.79(2H,m), 6.93(2H,d, J=8.7Hz), 7.38(2H,d,J=8.7Hz), 7.96(1H,m), 8.86(1H,d,J=6.6Hz), 9.02(1H,d,J=8.4Hz), 9.10(1H,S), 9.67(1H,d, J=8.7Hz), 12.59(1H,S), 5.94(1H,dd,J=4.8Hz,8.7Hz)

IR(Nujol)cm^{-1}:1760,1700,1665,1530,1500

(2) Compound 89b (1.31 g, 1.22 mmol) was dissolved in CH_2Cl_2 23 ml and $MeNO_2$ 6 ml and the mixture was stirred under cooling. Anisole (1.59 ml, 12eq) and 1mol $AlCl_3/MeNO_2$ (12.2 ml, 10eq) were added thereto and the mixture was stirred at 5°C for 1.5 hr. The reaction mixture was poured into a mixture of 0.25N HCl 30 ml and Et_2O 60 ml with stirring. The water layer was separated, washed with Et_2O 60 ml, and purified with HP-20. Lyophilization gave compound 90b (0.23 g, yield 25%).

^{1}H-NMR(D_2O) 6 :1.30(3H,t,J=7.2Hz), 2.40(2H,m), 3.17(2H,m), 3.31,3.64(2H,ABq,J=18.0Hz), 3.667(2H,S), 4.32 (2H,q,J=7.2Hz), 4.64(2H,t,J=7.5Hz), 5.23(1H,d,J=5.1Hz), 5.53(4H,m), 5.88(3H,m), 7.89(1H,dd,J=8.1Hz.6.3Hz), 8.79(1H,d,J=8.1Hz), 8.85(1H,d,J=6.3Hz), 8.87(1H,S)

IR(KBr)cm^{-1}:1774,1670,1613,1526,1488,1462

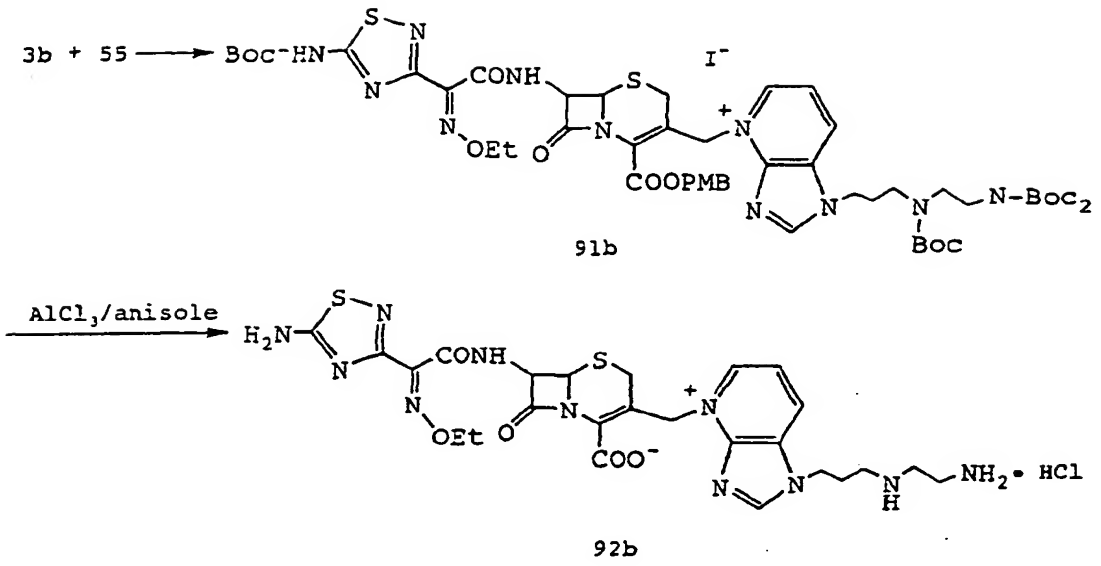
Elementary Analysis as $C_{26}H_{80}N_{10}O_5S_2 \cdot 1.0HCl, 5.0H_2O$

calc. : C,41.46:H,5.49; N,18.60; S,8.51; Cl,4.71

found: C,41.47; H,5.31; N,18.76; S,8.29; Cl,4.48

Example 21

[0205]



(1) Compound 55 (1.14 g, 2.19 mmol) of Reference Example 21 and compound 3b (2.0 g, 1.2eq) were dissolved in MeCN 20 ml and the mixture was stirred at room temperature for 3 hr. From the reaction mixture, MeCN was evaporated under reduced pressure and the residue was washed with Et_2O 50 ml to give compound 91b (2.64 g, yield 94%).

^{1}H-NMR(DMSO-d6) δ :1.24(3H,t,J=7.2Hz), 1.38(9H,S), 1.43(18H,S), 1.51(9H,S), 2.06(2H,m), 3.77(3H,S), 4.20 (2H,q,J=7.2Hz), 4.45(2H,m), 5.10(1H,d,J=5Hz), 5.29(2H,m), 5.60,6.11(2H,AB q,J=14.4Hz), 5.95(1H,dd,J=8.2Hz, 5Hz), 6.94(2H,d,J=8.6Hz), 7.39(2H,d,J=8.6Hz), 7.97(1H,m), 8.87(1H,d,J=5.4Hz), 9.05(1H,d,J=8.2Hz), 9.10(1H, S), 9.69(1H,d,J=8.2Hz), 12.61(1H,S)

IR(Nujol)cm^{-1}:1781,1715,1690,1545,1518

(2) Compound 91b (2.62 g, 2.05 mmol) was dissolved in CH_2Cl_2 40 ml and $MeNO_2$ 10 ml and the mixture was stirred under cooling. Anisole (2.67 ml, 12eq) and 1mol $AlCl_3/MeNO_2$ (20.5 ml, 10eq) were added thereto and the mixture was stirred at 5°C for 1.5 hr. The reaction mixture was poured into a mixture of 0.25N HCl 50 ml and Et_2O 100 ml with stirring. The water layer was separated, washed with Et_2O 100 ml and purified with HP-20. Lyophilization gave compound 92b (0.23 g, yield 14%).

^{1}H-NMR(D_2O) δ :1.31(3H,t,J=7Hz), 2.45(2H,m), 3.42(6H,m), 4.33(2H,q,J=7Hz), 4.66(2H,d,J=7.4Hz), 5.23(1H,d, J=5Hz), 5.61.5.91(2H,ABq,J=14.8Hz), 5.85(1H,d,J=5Hz), 7.89(1H,dd,J=8Hz,6.4Hz), 8.80(1H,d,J=8Hz), 8.84(1H, d,J=6.4Hz), 8.88(1H,S)

IR(KBr)cm^{-1}:1772,1668,1610,1524,1488,1462

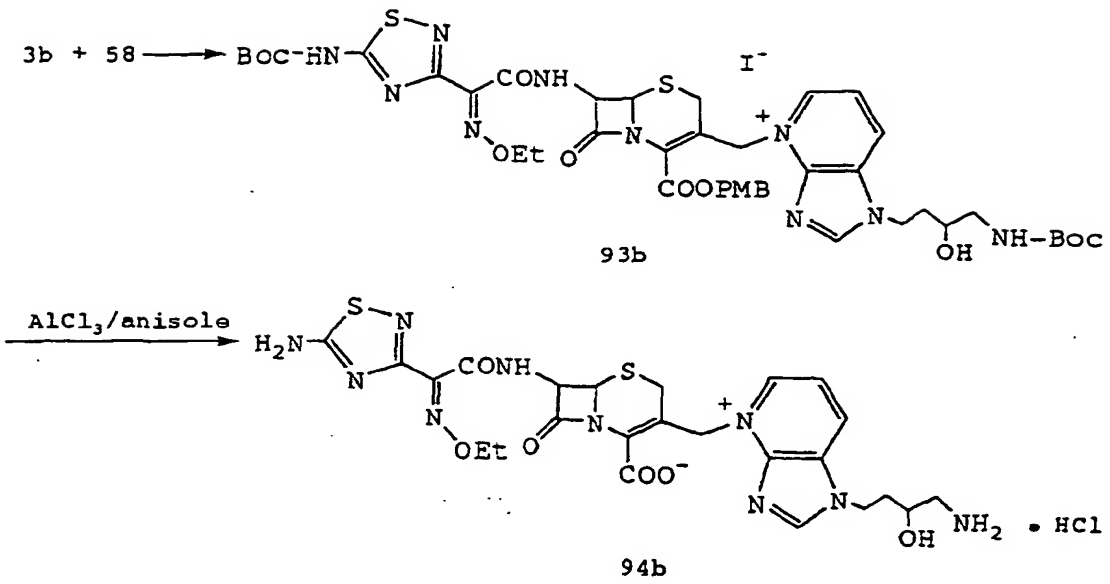
Elementary Analysis as $C_{25}H_{81}N_{11}O_5S_2 \cdot 2.2HCl, 5.0H_2O$

calc.: C,37.53; 11,5.44; N,19.26; S,8.02; Cl,9.75

found: C,37.53; H,5.41; N,19.47; S,7.96; C1,9.77

Example 22

[0206]



(1) Compound 58 (0.36 g, 1.17 mmol) of Reference Example 23 and compound 3b (1.07 g, 1.2eq) were dissolved in DMF 6 ml and the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was added to Et_2O 300 ml under stirring, then the precipitate was filtered to give compound 93b (1.14 g, yield 92%).

^{1}H-NMR(DMSO-d6) δ :1.24(3H,t,J=7.2Hz), 1.36(9H,S), 1.51(9H,S), 2.95(2H,m), 3.77(3H,S), 4.20(2H,q,J=7.2Hz), 4.55(2H,m), 4.95(1H,(1,J=,5.4Hz), 5.10(1H,d,3=5.2Hz), 5.29(2H,S), 5.58,6.11(2H,ABq,J=14.6Hz), 5.95(1H,dd, J=8.6Hz,5.2Hz), 6.94(2H,d,J=8.2Hz), 7.38(2H,d,J=8.2Hz), 7.95(1H,m), 8.85(1H,d,J=6.6Hz), 8.99(1H,d,J=8Hz), 9.68(1H,d,J=8.6Hz), 12.6(1H,S)

IR(Nujol)cm^{-1}:1785,1710,1695,1680,1550,1515

(2) Compound 93b (1.14 g, 1.07 mmol) was dissolved in CH_2Cl_2 20 ml and $MeNO_2$ 7 ml and the mixture was stirred under cooling. Anisole (1.40 ml, 12eq) and 1mol $AlCl_3/MeNO_2$ (10.7 ml, 10eq) were added thereto and the mixture was stirred at 5°C for 1.5 hr. The reaction mixture was poured into a mixture of 0.25N HCl 40 ml and Et_2O 80 ml. The water layer was separated, washed with Et_2O 80 ml, and purified with HP-20. Lyophilization gave compound 94b (0.35 g, yield 41%).

^{1}H-NMR(D_2O) δ :1.30(3H,t,J=7Hz), 2.20(2H,m), 3.20(2H,m), 3.31,3.63(2H,ABq,J=18.3Hz), 3.88(1H,m), 4.33(2H, q,J=7Hz), 4.69(2H,t,J=6.2Hz), 5.23(1H,d,J=5Hz), 5.64,5.90(2H,ABq,J=14.1Hz), 5.86(1H,d,J=5Hz), 7.87(1H,dd, J=8.2Hz,6.2Hz), 8.79(1H,d,J=8.2Hz), 8.82(1H,d,J=6.2Hz), 8.87(1H,S)

IR(KBr)cm^{-1}:1772,1673,1632,1523,1489,1462

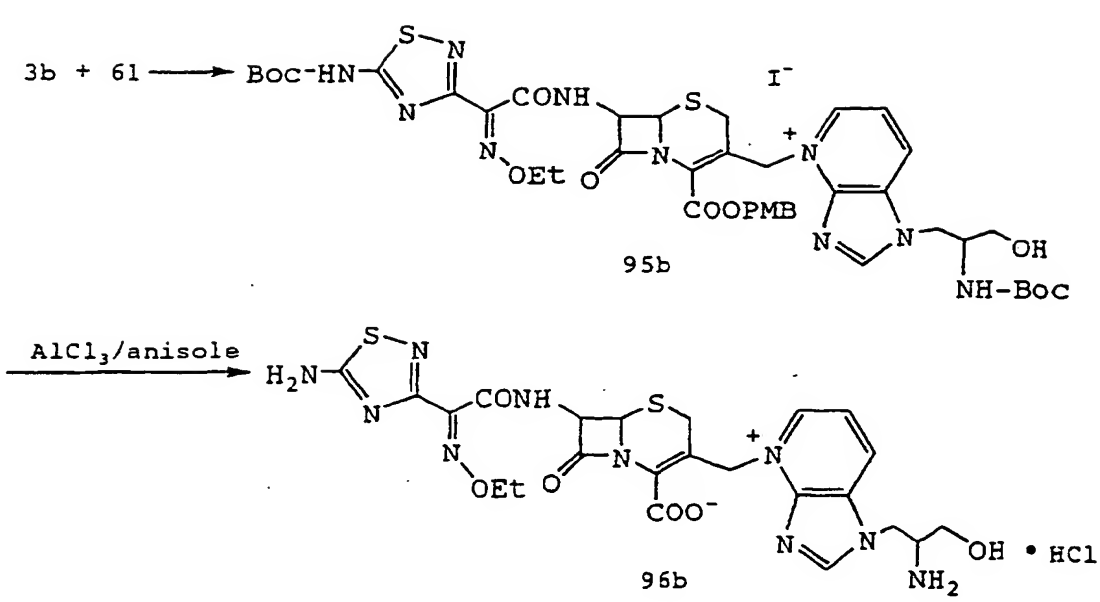
Elementary Analysis as $C_{24}H_{25}N_{10}O_6S_2 \cdot 1.5HCl,4.5H_2O$

calc. : C,38.30; H,5.17; N,18.61; S,8.52; Cl,7.07

found: C,38.30; H,5.00; N,18.57; S,8.29; Cl,6.92

Example 23

[0207]



(1) Compound 61 (0.392 g, 1.34 mmol) of Reference Example 25 and compound 3b (1.22 g, 1.2eq) was dissolved in DMF 7 ml and the mixture was stirred at room temperature for 1 hr. The reaction mixture was added to Et_2O 300 ml under stirring, then the precipitate was filtered to give compound 95b (1.33 g, yield 94%).

^{1}H-NMR(DMSO-d6) δ :1.23(3H,t,J=6.9Hz), 1.51(18H,S), 3.77(3H,S), 4.19(2H,q,J=6.9Hz), 5.61,6.09(2H,ABq, J=15.0Hz), 5.95(1H,dd,J=8.1Hz,5.0Hz), 6.95(2H,d,J=8.7Hz), 7.39(2H,d,J=8.7Hz), 8.01(1H,m), 8.88(1H,d, J=6.6Hz), 8.98(1H,d,J=10.8Hz), 9.67(1H,d,J=8.1Hz), 12.59(1H,S)

IR(Nujol)cm^{-1}:1785,1708,1680,1540,1515

(2) Compound 95b (1.31 g, 1.25 mmol) was dissolved in CH_2Cl_2 25 ml and $MeNO_2$ 8 ml and the mixture was stirred under cooling. Anisole (1.63 ml, 12eq) and 1mol $AlCl_3/MeNO_2$ (12.5 ml, 10eq) were added thereto and the mixture was stirred at 5°C for 1.5 hr. The reaction mixture was poured into a mixture of 0.25N HCl 50 ml and Et_2O 100 ml , then the water layer was separated, washed with Et_2O 100 ml, and purified with HP-20. Lyophilization gave compound 96b (0.29 g, yield 31%).

^{1}H-NMR(D_2O) δ :1.131(3H,t,J=7Hz), 3.33,3.64(2H,ABq,J=17.9Hz), 3.80(5H,m), 4.33(2H,q,J=7Hz), 4.88(2H,m), 5.23(1H,d,J=4.8Hz), 5.86(1H,d,J=4.8Hz).

5.65,5.96(2H,ABq,J=14.5Hz), 7.92(1H,dd,J=8.2Hz,6.6Hz), 8.86(1H,d,J=8.2Hz), 8.89(1H,d,J=6.6Hz), 8.92(1H,S)

IR(KBr)cm^{-1}:1772,1633,1523,1488,1463

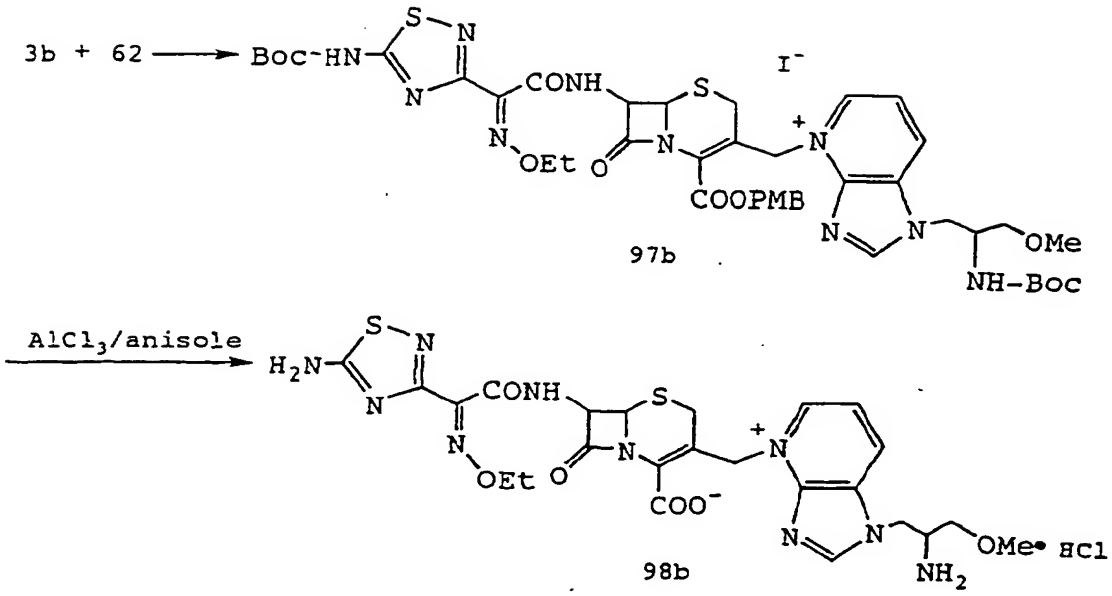
Elementary Analysis as $C_{23}H_{26}N_{10}O_6S_2 \cdot 1.5HCl, 4.6H_2O$

calc. :C,37.31; H,5.01; N,18.92; S,8.66; Cl,7.19

found: C,37.33; H,4.93; N,18.93; S,8.58; Cl,7.32

Example 24

[0208]



(1) Compound 62 (0.36 g, 1.18 mmol) of Reference Example 26 and compound 3b (1.07 g, 1.2eq) were dissolved in DMF 8 ml and the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was added to Et_2O 300 ml under stirring, then the precipitate was filtered to give compound 97b (1.26 g, yield 100%).

^{1}H-NMR(DMSO-d6) δ :1.23(3H,t,J=6.8Hz), 1.51(18H,S), 3.77(3H,S), 4.20(2H,q,J=6.8Hz), 6.94(2H,d,J=7Hz), 7.39 (2H,(d,J=7Hz), 8.0(1H,m), 8.73(1H,m), 8.90(1H,S), 8.98(1H,(1,J=8.6Hz), 9.68(1H,d,J=8.4Hz), 12.61(1H,S)

IR(Nujol)cm^{-1}:1785,1710,1690,1550,1515

(2) Compound 97b (1.65 g, 1.69 mmol) was dissolved in CH_2Cl_2 30 ml and $MeNO_2$ 10 ml and the mixture was stirred under cooling. Anisole (2.20 ml, 12eq) and 1mol $AlCl_3/MeNO_2$ (16.9 ml, 10eq) were added thereto and the mixture was stirred at 5°C for 1.5 hr. The reaction mixture was poured into a mixture of 0.25N HCl 60 ml and Et_2O 120 ml , then the water layer was separated, washed with Et_2O 120 ml, and purified with HP-20. Lyophilization gave compound 98b (0.26 g, yield 21%).

^{1}H-NMR(D_2O) δ :1.30(3H,t,J=7Hz), 3.33,3.64(2H,ABq,J=18.8Hz), 3.41(3H,S), 3.65(2H,m), 3.14(1H,m), 4.33(2H, q,J=7Hz), 4.89(2H,d,J=7Hz), 5.23(1H,d,J=4.6Hz), 5.67,5.96(2H,ABq,J=14.9Hz), 5.86(1H,d,J=4.6Hz), 7.93(1H, dd,J=8.2Hz,6.4Hz), 8.83(1H,d,J=8.2Hz), 8.89(1H,d,J=6.4Hz), 8.91(1H,S)

IR(KBr)cm^{-1}:1774,1671,1633,1524,1488,1463

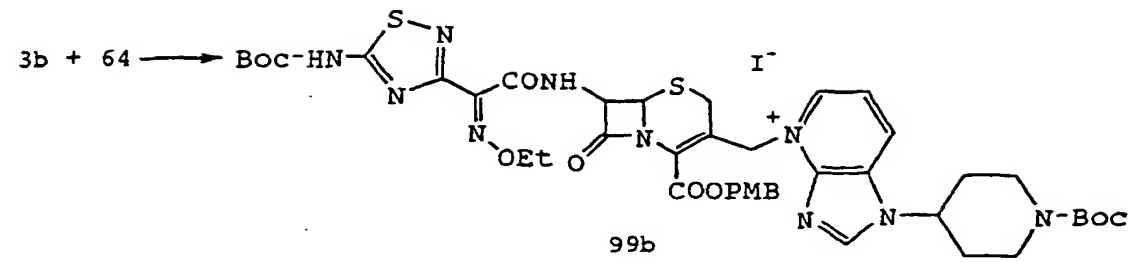
Elementary Analysis as $C_{24}H_{28}N_{10}O_6S_2 \cdot 1.6HCl, 4.0H_2O$

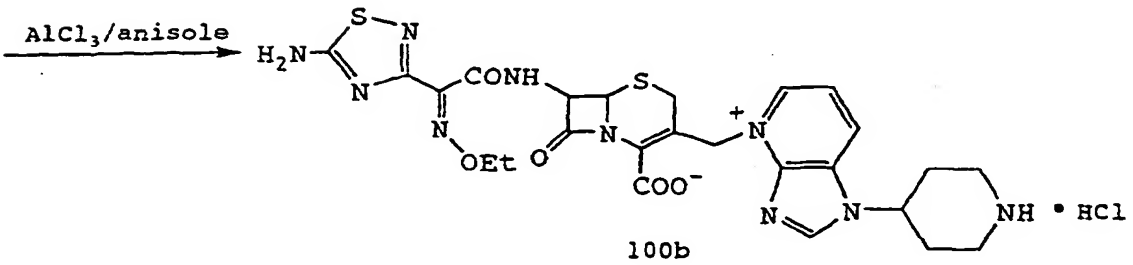
calc. :C,38.58; H,5.08; N,18.75; S,8.58; Cl,7.59

found: C,38.61; H,5.00; N,18,57; S,8.34; Cl,7.56

Example 25

[0209]

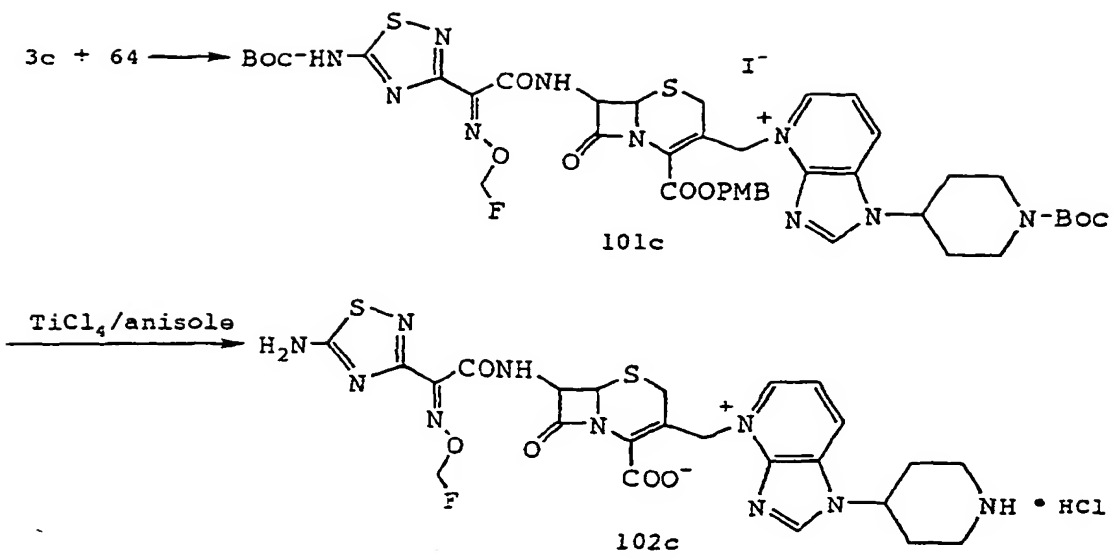




(1) Compound 64 (0.96 g, 3.17 mmol) of Reference Example 27 and compound 3b (2.89 g, 1.2eq) were dissolved in DMF 13 ml and the mixture was stirred at room temperature for 1 hr. The reaction mixture was added to Et_2O 500 ml under stirring, then the precipitate was filtered to give compound 99b (3.36 g, yield 100%).
^{1}H-NMR(DMSO-d6) δ : 1.24(3H,t,J=7Hz), 1.45(9H,S), 1.50(9H,S), 3.76(3H,S), 4.20(2H,q,J=7Hz), 5.11(1H,d, J=4.2Hz), 5.29(2H,S), 5.56,6.11(2H.ABq,J=14.6Hz), 5.94(1H,dd,J=8.2Hz,4.2Hz), 6.94(2H,d,J=8.6Hz), 7.39(2H,d, J=8.6Hz), 7.95(1H,m), 8.76(1H,d,J=6.4Hz), 9.10(1H,d,J=8.2Hz), 9.18(1H,S), 9.67(1H,d,J=8.2Hz), 12.59(1H,S)
IR(Nujol)cm^{-1}:1785,1710,1665,1545
(2) Compound 99b (3.36 g, 3.17 mmol) was dissolved in CH_2Cl_2 75 ml and $MeNO_2$ 35 ml and the mixture was stirred under cooling. Anisole (4,13 ml, 12eq) and 1mol $AlCl_3/MeNO_2$ (31.7 ml, 10eq) were added thereto and the mixture was stirred at 5°C for 1.5 hr with stirring. The reaction mixture was poured into a mixture of 0.25N HCl 130 ml and Et_2O 260 ml, then the water layer was separated, washed with Et_2O 260 ml, and purified with HP-20. Lyophilization gave compound 100b (0.62 g, yield 25%).
^{1}H-NMR(D_2O) δ :1.30(3H,t,J=7.5Hz), 2.50(4H,m), 3.33(3H,m), 3.70(3H,m), 4.33(2H,q,J=7.5Hz), 5.07(1H,m), 5.23 (1H,d,J=4.8Hz), 5.64,5.91(2H,ABq,J=14.7Hz), 5.85(1H,d,J=4.8Hz), 7.89(1H,m)8.85(2H,m), 8.98(1H,S)
IR(KBr)cm^{-1}:1773,1670,1616,1524,1460
Elementary Analysis as $C_{25}H_{28}N_{10}O_5S_2 \cdot 1.4HCl, 4.3H_2O$
calc. :C,40.51; H,5.17; N,18.90; S,8.65; Cl,6.70
found: C,40.52; H,5.20; N,18.91; S,8.48; Cl,6.48

Example 26

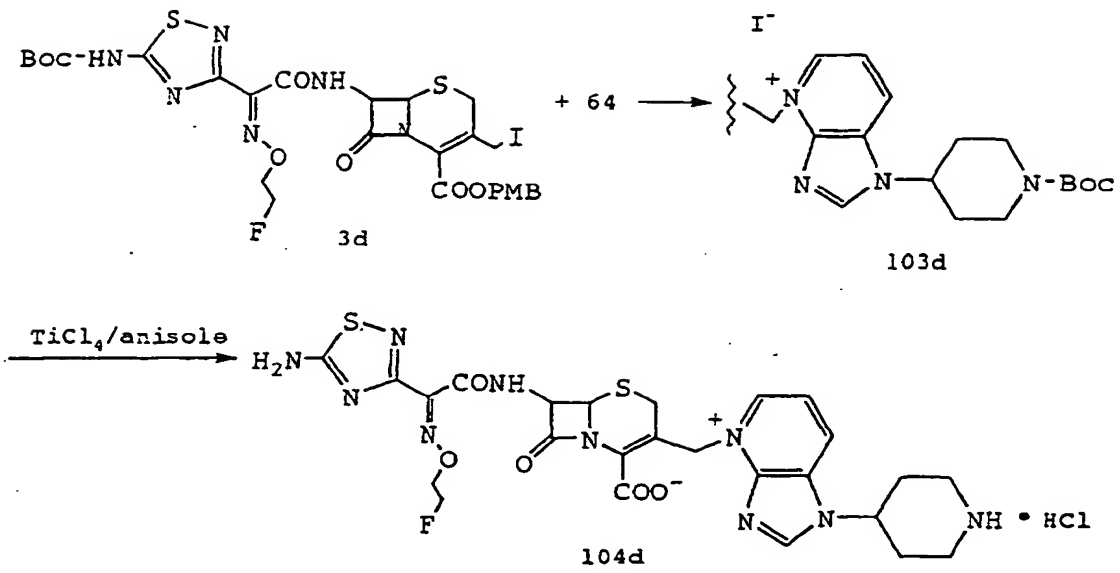
[0210]



(1) Compound 64 (0.454 g, 1,5 mmol) of Reference Example 27 and compound 3c (1.37 g, 1.2eq) were dissolved in DMF 6 ml and the mixture was stirred at room temperature for 1 hr. The reaction mixture was added to Et_2O 300 ml, then the precipitate was filtered to give compound 101c (1.64 g, yield 100%),
^{1}H-NMR(DMSO-d6) δ :1.44(9H,S), 1.51(9H,S), 2.10(4H,m), 3.77(3H,S), 4.19(1H,m), 5.12(1H,d,J=4.6z), 5.29(2H, S), 5.57,6.10(2H,ABq,J=13.6Hz), 6.93(2H,d,J=9Hz), 7.38(2H,d,J=9Hz), 7.95(1H,m), 8.86(1H,d,J=5.8Hz), 9.10 (1H,d,J=7.8Hz), 12.68(1H,S)
IR(Nujol)cm^{-1}:1790,1715,1690,1665,1550
(2) Compound 101c (1.62 g, 1.52 mmol) was dissolved in CH_2Cl_2 27 ml and $MeNO_2$ 14 ml and the mixture was stirred under cooling. Anisole (1.98 ml) and $TiCl_4$ (1.67 ml, 10eq) were added thereto and the mixture was stirred at 5°C for 1.5 hr. The reaction mixture was poured into a mixture of 0.25N HCl 80 ml and Et_2O 160 ml, then the water layer was separated, washed with Et_2O 160 ml, and purified with HP-20. Lyophilization gave compound 102c (0.35 g, yield 30%).
^{1}H-NMR(D_2O) δ :2.50(4H,m), 3.34(3H,m), 3.70(3H,m), 5.05(1H,m), 5.23(1H,d,J=5Hz), 5.65,5.90(2H,ABq, J=16.6Hz), 5.82(2H,d,J=54,4Hz), 5.84(1H,d,J=5Hz), 7.87(1H,dd,J=8.2Hz,6.2Hz), 8.81(1H,d,J=8.2Hz), 8.87(1H, d,J=6.2Hz), 8.99(1H,S)
IR(KBr)cm^{-1}:1774,1674,1616,1525,1460
Elementary Analysis as $C_{24}H_{25}N_{10}O_5S_2F \cdot 1.5HCl,2.6H_2O$
calc. : C,40.13; H,4.46; N,19.50; S,8.93; F,2.65; Cl,7.41
found: C,40.16; H,4.48; N,19.46; S,7.69; F,2.15; Cl,7.18

Example 27

[0211]



(1) Compound 64 (0.454 g, 1.5 mmol) of Reference Example 27 and compound 3d (1.51 g, 1.3 eq.) were dissolved in DMF 8 ml and the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was added to Et_2O 300 ml under stirring, then the precipitation was filtered to give compound 103d (1.68 g, yield 100%).

^{1}H-NMR(DMSO-d6) δ :1.44(9H,S), 1.50(9H,S), 3.77(3H,S), 5.10(1H,d,J=5z), 5.29(2H,S), 5.57,6.12(2H,ABq, J=14.6Hz), 5.95(1H,dd,J=8.6Hz,5Hz), 6.94(2H,d,J=8.6Hz), 7.39(2H,d,J=8.6Hz), 7.96(1H,m), 8.87(1H,d, J=5.8Hz), 9.10(1H,(1,J=8.6Hz), 9.18(1H,S), 9.74(1H,d,J=8.6Hz), 12.62(1H,S)

IR(Nujol)cm^{-1}:1790,1719,1695,1680,1665,1555,1540,1519

(2) Compound 103d (1.66 g, 1.54 mmol) was dissolved in CH_2Cl_2 27 ml and $MeNO_2$ 14 ml and the mixture was stirred under cooling. Anisole (2.01 ml, 12eq) and $TiCl_4$ (1.69 ml, 10eq) were added thereto and the mixture was stirred at 5°C for 1.5 hr. The reaction mixture was poured into a mixture of 0.25N HCl 80 ml and Et_2O 160 ml, then the water layer was separated, washed with Et_2O 160 ml, and purified with HP-20. Lyophilization gave compound 104d (0.35 g, yield 29%).

^{1}H-NMR(D_2O) δ :2.50(4H,m), 3.35(3H,m), 3.69(3H,m), 5.25(1H,d,J=4.6Hz), 5.71,5.94(2H,ABq,J=14.8Hz), 5.87 (1H,d,J=4.6Hz), 7.89(1H,dd,J=8.2Hz,6.4Hz), 8.84(1H,d,J=8.2Hz), 8.88(1H,d,J=6.4Hz), 9.00(1H,S)

IR(KBr)cm^{-1}:1774,1671,1615,1524,1460

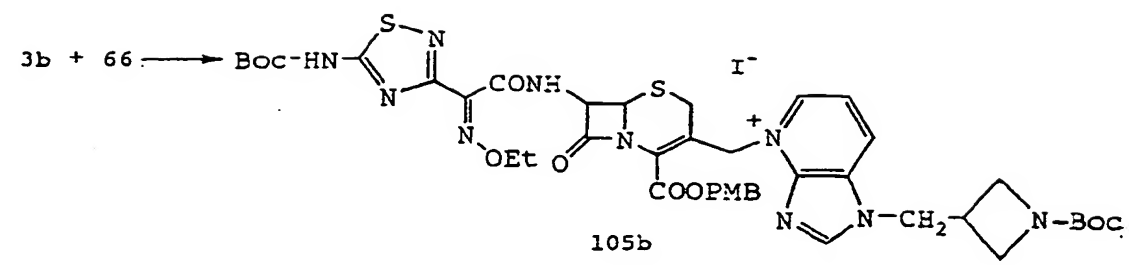
Elementary Analysis as $C_{25}H_{27}N_{10}O_5S_2F \cdot 1.6HCl, 4.8H_2O$

calc. : C,38.71; H,4.97; N,18.06; S,8.27; F,2.45; Cl,7.32

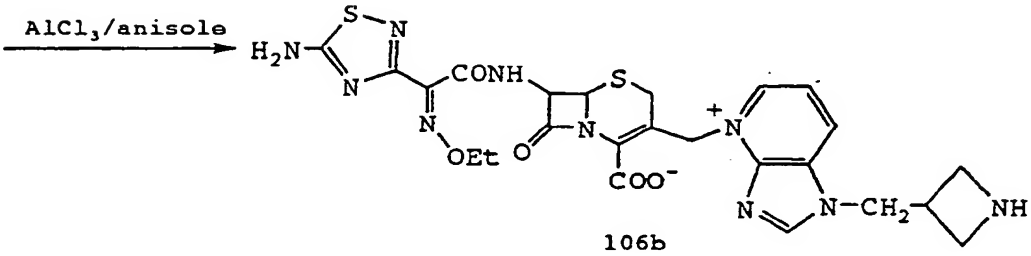
found: C,38.73; H,4.93; N,17.82; S,8.10; F,2.29; Cl,7.23

Example 28

[0212]



105b



106b

(1) Compound 66 (0.41 g, 1.42 mmol) of Reference Example 28 and compound 3b (1.29 g, 1.2eq) were dissolved in DMF 10 ml and the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was added to Et_2O 300 ml under stirring, then the precipitate was filtered to give compound 105b (1.38 g, yield 93%).

^{1}H-NMR(DMSO-d6) δ :1.23(3H,t,J=7Hz), 1.38(9H,S), 1.50(1H,S), 3.77(3H,S), 4.19(2H,q,J=7Hz), 5.09(1H,d, J=5.2Hz), 5.57,6.10(2H,ABq,J=14.6Hz), 5.94(1H,dd,J=8.2Hz,4.6Hz), 6.94(2H,d,J=8.6Hz), 7.39(2H,d,J=8.6Hz), 7.95(1H,m), 8.86(1H,(1,J=6.2Hz), 9.08(1H,d,J=8.2Hz), 9.68(1H,d,J=8.2Hz), 12.6(1H,S)

IR(Nujol)cm^{-1}:1790,1715,1680,1550,1520

(2) Compound 105b (1.36 g, 1.3 mmol) was dissolved in CH_2Cl_2 24 ml and $MeNO_2$ 8 ml and the mixture was stirred under cooling. Anisole (1.69 ml, 12eq) and 1mol $AlCl_3/MeNO_2$ (13 ml, 10eq) were added thereto and the mixture was stirred at 5°C for 1.5 hr. The reaction mixture was poured into a mixture of 0.25N HCl 50 ml and Et_2O 100 ml, then the water layer was separated, washed with Et_2O 100 ml, and purified with HP-20. Lyophilization gave compound 106b (0.30 g, yield 31%).

^{1}H-NMR(D_2O) δ :1.30(3H,t,J=7Hz), 3.31,3.64(2H,ABq,J=17.6Hz), 5.23(1H,d,J=4.6Hz), 5.64,5.91(2H,ABq, J=15.4Hz), 5.86(1H,d,J=4.6Hz), 7.90(1H,dd,J=7.8Hz,6.4Hz), 8.80(1H,d,J=7.8Hz), 8.86(1H,d,J=6.4Hz), 8.89(1H, S)

IR(KBr)cm^{-1}:1773,1670,1616,1524,1487,1463,1450

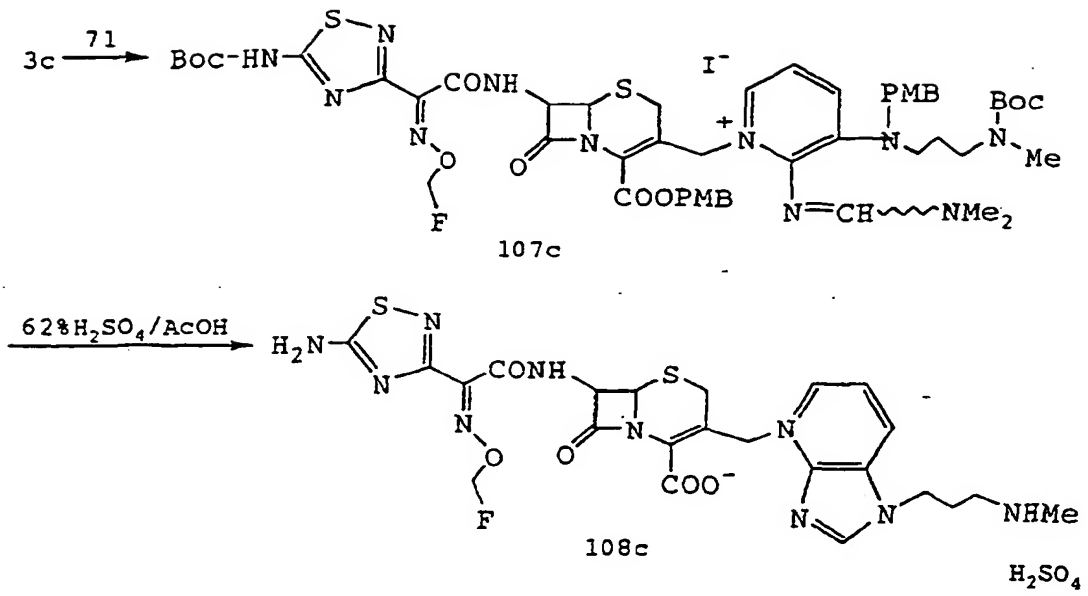
Elementary Analysis as $C_{24}H_{26}N_{10}O_5S_2 \cdot 1.6HCl \cdot 4.6H_2O$

calc. :C,38.95; H,5.02; N,18.93; S,8.67; Cl,7.67

found: C,38.92; H,5.08; N,18.65; S,8.33; Cl,7.55

Example 29

[0213]



(1) Compound 3c (19.1 g, 25 mmol) and compound 71 (14.4 g, 1.2eq) of Reference Example 31 were dissolved in DMF 40 ml and the mixture was stirred at room temperature for 2.5 hr. The reaction mixture was poured into 5% brine, then the precipitate was filtered, dried, and washed with AcOEt to give compound 107c (27.4 g, yield 96%).

^{1}H-NMR(DMSO-d6) δ :1.32(9H,S), 1.51(9H,S), 2.71(3H,S), 2.89(3H,S), 3.10(3H,S), 3.72(3H,S), 3.76(3H,S), 4.02 (2H,m), 5.10(1H,d,J=4.8Hz), 5.20(4H,m), 5.82(2H,d,J=54.6Hz), 5.96(1H,dd,J=8.1Hz,4.8Hz), 6.87(2H,q,J=8.4Hz), 6.95(2H,d,J=8.7Hz), 7.00(2H,d,J=8.4Hz), 7.38(2H,d,J=8.7Hz), 7.22(1H,m), 7.78(1H,m), 8.16(1H,m), 8.43(1H,m)
IR($CHCl_3$)cm^{-1}:1775,1720,1695,1640,1555,1520

(2) A solution of compound 107c (9.99 g, 8.2 mmol) in AcOH 18 ml was added to 62% H_2SO_4 42 ml under keeping the reaction temperature at 5°C. After stirring at 5°C for 1 hr, the reaction mixture was poured into i-PrOH, then the precipitate was filtered and dried under reduced pressure. The obtained precipitate was purified with HP-20 and crystallized from dil. H_2SO_4 to give compound 108c (1.90 g, yield 27%) as 1 sulfate 8-hydrate crystals.

^{1}H-NMR(D_2O) δ :2.42(2H,m), 2.73(3H,S), 3.17(2H,t,J=7.6Hz), 3.30,3.64(2H,ABq,J=18.3Hz), 4.62(2H,t,J=7.4Hz), 5.25(1H,d,J=4.8Hz), 5.70,5.91(2H,ABq,J=13.0Hz), 5.82(2H,d,J=54.6Hz), 5.86(4.8Hz), 7.87(1H,dd,J=8.2Hz, 6.4Hz), 8.80(1H,d,J=8.2Hz), 8.83(1H,d,J=6.4Hz), 8.88(1H,S)
IR(Nujol) δ : 1774,1720,1679,1631,1577,1529,1495,1463,1417
Elementary Analysis as $C_{23}H_{25}N_{10}O_5S_2F$: 1.0 H_2SO_4 · 8.2 H_2O (calculated water content: 17.02%)
calc. :C,32.48; H,5.14; N,16.47; S,11.31; F,2.23
found: C,32.57; H,5.00; N,16.49; S,11.31; F,2.22

(3) An aqueous solution (45 ml) of the 8-hydrate crystal (31.7 g) obtained above (2) was subjected to HP-20 chromato with 0.001N HCl aq., and the eluted solution was mixed with poly(4-vinylpyridine) resin to adjust the pH to 4. then which was filtered. The filtrate was concentrated under reduced pressure up to100 g, which was stirred under ice-cooling, then 2N H_2SO_4 was added thereto so as to adjust the pH to 1.5, whereby crystals were precipitated. After allowing to stand over night, the crystal was filtered, washed with cooled H_2O and cooled H_2O-EtOH successively, and dried under reduced pressure to give 1 sulfate 7-hydrate crystal of compound 108c 14 g.
Water content (KF: 15.43% Calc.: 15.21%)
The diffraction pattern of the 7-hydrate crystal is shown in Table A.

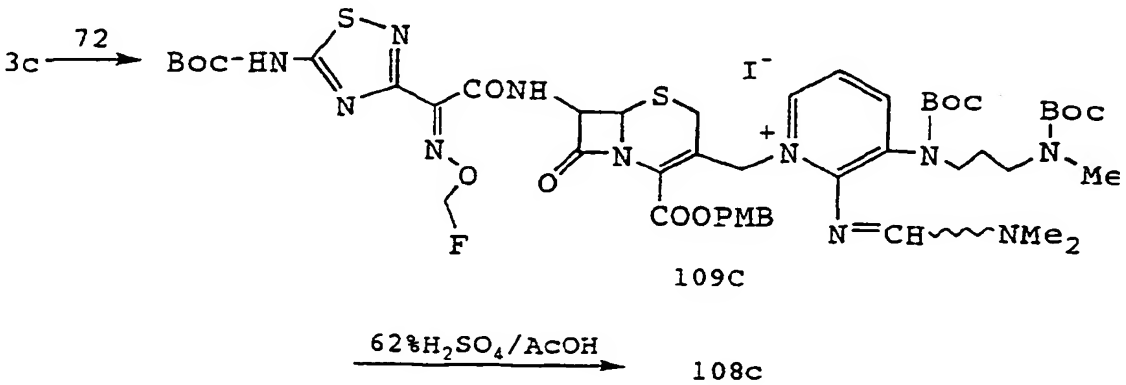
(Table A)

2θ	I	2θ	I
8.02	162	22.20	250
9.62	178	24.20	268
11.58	290	24.68	170
13.82	288	25.12	360
14.26	242	26.26	475
15.84	572	27.56	318
19.40	338	28.68	302
20.22	215	29.90	555
20.40	222	38.40	388
21.20	272		
2 θ = diffraction angle (unit: degree) , I =intensity (measuring condition) Tube:Cu; Voltage:40KV; Current:40mA; Scanning :3.0 ° /min; Step:0.02 °; Sampling angle:5 ° ;Termination angle:40°			

[0214] The above 1 sulfate·7 hydrate crystal, i.e., compound 108c-2, has an inclination to become stable as 4- to 5-hydrate (calculated water content: 9.30~11.36%) upon dehydration. The crystals of 4- to 7-hydrate are deemed to show main peaks of the same diffraction pattern (2θ) as above. provided that the intensity (I) may be varied depending on the water content. The storage stability of vial preparations containing each crystal was examined to result in the order of stability: 4- to 5-hydrate > 7-hydrate > 8-hydrate.

Example 30

[0215]



(1) Compound 3c (19.1 g, 25 mmol) of Reference Example 32 and compound 72 (13.2 g, 1eq) were dissolved in DMF 40 ml and the mixture was stirred at room temperature for 17 hr. The reaction mixture was poured into diisopropylether. then the precipitated oily product was separated and dried under reduced pressure to give compound 109c (34.4 g, yield 100%).

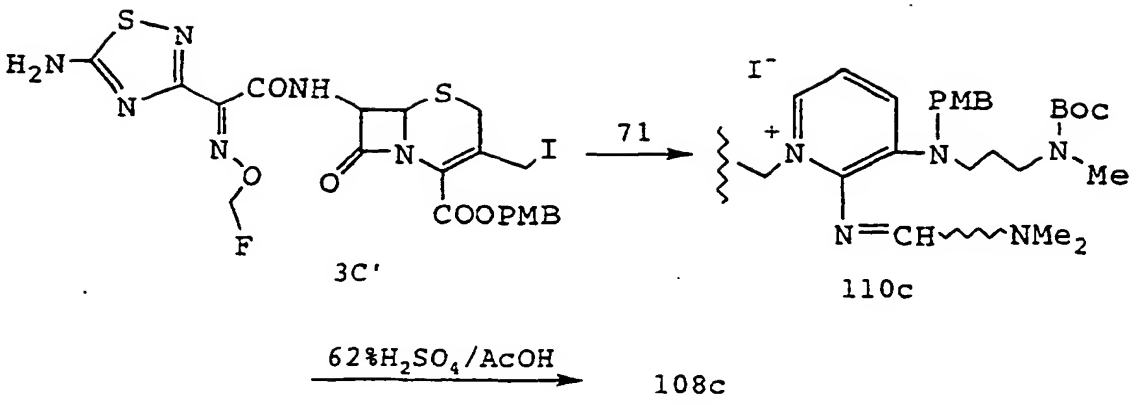
^{1}H-NMR(DMSO-d6) δ :1.38(18H,S), 1.51(9H,S), 2.78(3H,S), 2.95(3H,S), 3.08(3H,S), 3.76(3H,S), 5.21(5H,m), 5.82(2H,d,J=55.6Hz), 5.95(1H,m), 6.95(2H,d,J=8Hz), 7.38(2H,d,J=8Hz), 7.73(1H,m), 8.24(1H,m), 8.49(1H,m)

IR($CHCl_3$)cm^{-1}:1775,1720,1770,1640,1550,1520,1400

(2) The same procedure as that of Example 29(2), using compound 109c (9.7 g, 8.2 mmol), AcOH 18 ml, and 62% H_2SO_4 42ml, gave the above compound 108c (1.93 g, yield 28%).

Example 31

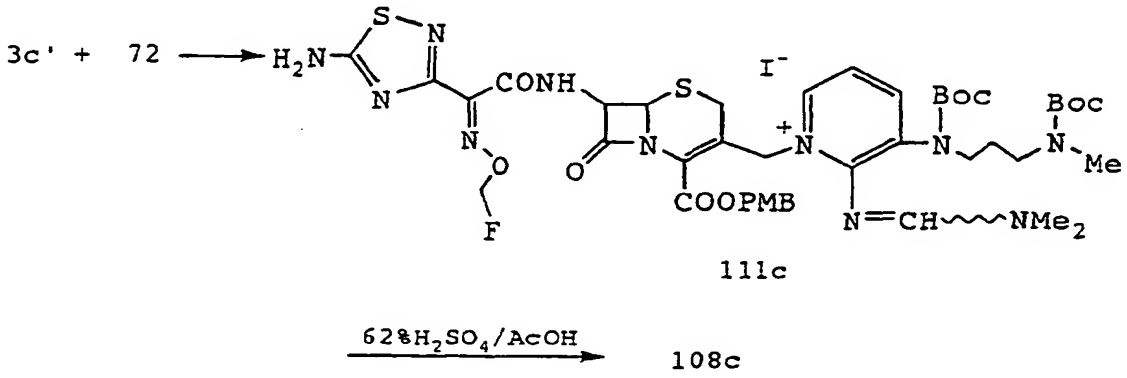
[0216]



(1) Compound 3c' (25.6 g, 38.7 mmol) and compound 71 (22.3 g, 1.2eq) of Reference Example 31 were dissolved in dimethylacetoamide 50ml and the mixture was stirred at room temperature for 3.5 hr. The reaction mixture was poured into t-butyl acetate and the precipitate was filtered to give compound 110c (51.1 g, yield 100%).
^{1}H-NMR(DMSO-d6) δ :1.32(9H,S), 1.56(2H,m), 2.70(3H,S), 2.79(3H,S). 3.10(3H,S), 3.72(3H,S), 3.76(3H,S), 4.00 (2H,m), 5.08(1H,d,J=4.7Hz), 5.21(5H,m), 5.60(3H,m), 5.91(3H,m), 6.96(5H,m), 7.20(1H,m), 7.37(4H,d,J=8.7Hz), 7.78(1H,m), 8.18(2H,m), 9.79(1H,d,J=8.3Hz)
IR($CHCl_3$)cm^{-1}:1785,1720,1685,1640,1620,1520,1400
(2) The same procedure as carried out in compound 110c (4.58 g, 4.1 mmol), AcOH 9 ml and 62% H_2SO_4 21ml, gave compound 108c (1.70 g, yield 49%).

Example 32

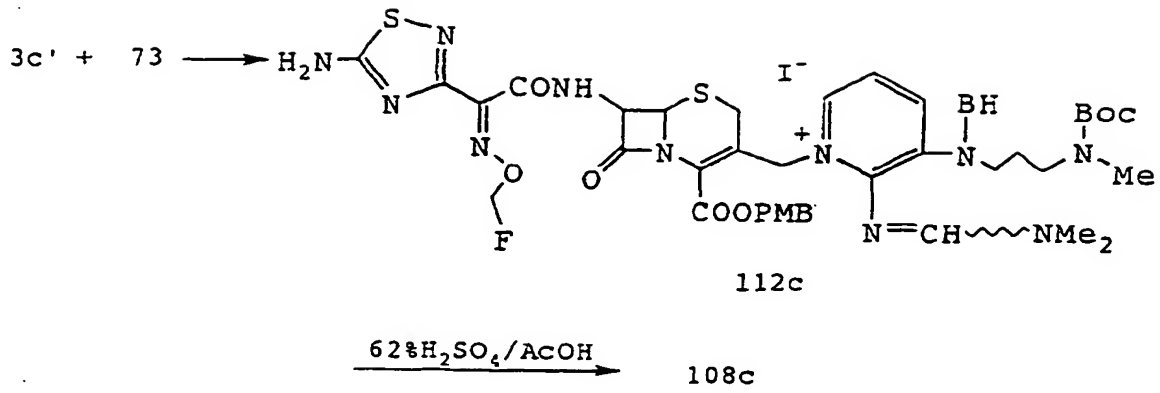
[0217]



(1) Compound 3c' (18.15 g, 27.4 mmol) and compound 72 (13.1 g, 1.1eq) of Reference Example 32 were dissolved in dimethylacetamide 40 ml and the mixture was stirred at room temperature for 17 hr. The reaction mixture was poured in 5% brine and the precipitate was filtered to give compound 111c (30.8 g, yield 100%).
^{1}H-NMR(DMSO-d6) δ :1.39(18H,S), 1.69(2H,m), 2.79(3H,S), 9.25(3H,S), 3.08(3H,S), 3.76(3H,S), 5.24(5H,m), 5.77(2H,d,J=55.5Hz), 5.91(2H,m), 6.95(2H,d,J=8.6Hz), 7.38(2H,d,J=8.6Hz), 7.74(1H,S), 8.22(2H,m), 8.50(1H,m)
IR($CHCl_3$)cm^{-1}:1790,1695,1645,1520,1400
(2) The same procedure as that of Example 29(2), using compound 111c (9.00 g, 8.2 mmol), AcOH 18 ml, and 62% H_2SO_4 42 ml, gave the above compound 108c (3.70 g, yield 53%).

Example 3 3

[0218]



112c

$\xrightarrow{62\%H_2SO_4/AcOH}$ 108c

(1) To a solution of compound 73 (502 mg, 1mmol) of Reference Example 33 in dimethylacetamide 1.2 ml, was added a solution of compound 3c' (662 mg, 1eq) in dimethylacetamide 1.2 ml and the mixture was stirred at room temperature for 8 hr. The reaction mixture was poured in 5% brine, then the precipitate was filtered and dried to give compound 112c (1.11 g, yield 95%).

^{1}H-NMR(DMSO-d6) δ :1.28(9H,S), 2.70(3H,S), 2.90(3H,S), 3.05(3H,S), 3.76(3H,S), 5.15(1H,d,J=4.8Hz), 5.20(3H, m), 5.57(3H,m), 5.78(2H,d,J=55.2Hz), 5.92(1H,dd,J=8.4Hz,4.8Hz), 6.94(2H,d,J=8.4Hz), 7.20 - 7.39(13H,m), 7.70 (1H,m), 8.23(2H,m), 8.43(1H,S)

IR($CHCl_3$)cm^{-1}:1780,1675,1635,1605,1510

(2) The same procedure as carried out in Example29(2), using compound 112c (2.63 g, 2.25 mmol), AcOH 5.2 ml, and 62% H_2SO_4 16g, gave the above compound 108c (0.96 g, yield 50%).

Example 34

[0219] A variety of compound (I) was further synthesized according to the above general method (2). The structure of compound (I) and the aforementioned synthesis methods A to F of compound (IV), a material for the 3-side chain, are shown in Table 1, with the NMR, IR, and Elementary Analysis in Tables 2 to 4.

(Table 1−1)

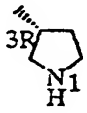
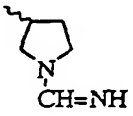
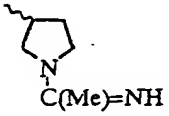
Compound (I) R1=amino R3=H (providedR3=Mein compound 246b)

No.	X	R2	R4	R5	Method of 3-side chain
211b	N	Et	(s) $CH_2CH^*(NH_2)Me$	H	C
211c	N	CH_2F	(s) $CH_2CH^*(NH_2)Me$	H	C
212c	N	CH_2F	$(CH_2)_3N(Me)CO_2{}^tBu$	H	E
213b	N	Et	$CH_2C(Me)_2NH_2$	H	B
214b	N	Et	$(CH_2)_2NHMe$	H	C
214c	N	CH_2F	$(CH_2)_2NHMe$	H	C
215d	N	CH_2 -CH_2F	$(CH_2)_3NH(CH_2)_2$ -OSO3H	H	E
216d	N	CH_2 -CH_2F	$(CH_2)_3NH(CH_2)_2OH$	H	E
216b	CH	Et	$(CH_2)_3NH(CH_2)_2OH$	H	E
216g	N	H	$(CH_2)_3NH(CH_2)_2OH$	H	E
220b	N	Et	H	Me	D
221b	N	Et	$(CH_2)_3NH_2$	Me	C
221c	N	CH_2F	$(CH_2)_3NH_2$	Me	C
221d	N	CH_2 -CH_2F	$(CH_2)_3NH_2$	Me	C
221a	N	Me	$(CH_2)_3NH_2$	Me	C
222b	N	Et	$(CH_2)_3NHMe$	Me	C
222c	N	CH_2F	$(CH_2)_3NHMe$	Me	C
223c	N	CH_2F	$(CH_2)_3NH$ -$(CH_2)_2OH$	Me	C
224b	N	Et	$(CH_2)_2NHMe$	Me	A
224c	N	CH_2F	$(CH_2)_2NHMe$	Me	C

(Table 1 — 2)

No.	X	R2	R4	R5	Method of 3-side chain
225c	N	CH_2F	$(CH_2)_3NH_2$	Et	C
226b	N	Et	$(CH_2)_3NHMe$	Et	C
226c	N	CH_2F	$(CH_2)_3NHMe$	Et	C
227c	N	CH_2F	$(CH_2)_3NHMe$	CF_3	C
231b	N	Et	H	OH	D
232b	N	Et	H	NH_2	C
233b	N	Et	H	$(CH_2)_3NH_2$	D
234b	N	Et	Me	$(CH_2)_3NH_2$	E
234c	N	CH_2F	Me	$(CH_2)_3NH_2$	E
240b	N	Et	$(CH_2)_2OH$	H	A
240c	N	CH_2F	$(CH_2)_2OH$	H	A
241b	N	Et	CHF_2	H	A
241c	N	CH_2F	CHF_2	H	A
241g	N	H	CHF_2	H	A
242b	N	Et	$CH_2CH=CH_2$	H	A
242c	N	CH_2F	$CH_2CH=CH_2$	H	A
243b	N	Et	CH_2OMe	H	A
244b	N	Et	$(CH_2)_3Cl$	H	A

(Table 1 — 3)

No.	X	R2	R4	R5	Method of 3-side chain
245b	N	Et	-(CH2)$_3$NH- 	H	E
246b*1	N	Et	Me	H	C
250b	N	Et		H	A
250c	N	CH_2F		H	A
251b	N	Et		H	A
252b	N	Et		H	E
253b	N	Et		H	E
254b	N	Et		H	E
255c	N	CH_2F	-R4-R5- = -(CH$_2$)$_3$-N(Me)-		F

(*1) R3 is p—Me for N^+.

(Table 2—1)

No.	^{1}H-NMR (D_2O) δ:
211b	1.31 (3H, d, J = 7.2 Hz), 1.45 (3H, d, J = 6.6 Hz), 3.32 and 3.63 (2H, ABq, J = 18Hz), 4.07 (1H, q like, J = 6.6 Hz), 4.36 (2H, q, J = 7.2Hz), 4.8 (2H, m), 5.22 (1H, d, J = 4.5 Hz), 5.63 and 5.93 (2H, ABq, J = 14.7Hz), 5.86(1H, d, J = 4.5Hz),7.93 (1H, dd, J = 6.6, 7.5Hz), 8.84 (1H, d, J = 7.5Hz), 8.88 (1H, d, J = 6.6Hz), 8.92 (1H, s).
211c	1.44 (3H, d, J = 6.6 Hz), 3.29 and 3.64 (2H, ABq, J = 18Hz), 4.06 (1H, q like, J = 6.6 Hz), 4.36 (2H, q, J = 7.2Hz), 4.8 (2H, m), 5.23 (1H, d, J = 4.8 Hz), 5.63 and 5.92 (2H, ABq, J = 14.7Hz), 5.82(2H, J = 54.3Hz), 5.86(1H, d, J = 4.8Hz), 7.91 (1H, dd, J = 6.6, 8.4Hz), 8.83 (1H, d, J = 8.4Hz), 8.89 (1H, d, J = 6.6Hz),
212c	[D6-DMSO]: 1.34 (9H, br s), 2.07-2.16 (2H, t-like), 2.79 (3H, s), 2.96 and 3.55 (2H, ABq, J = 18Hz), 3.24 (2H, t, J = 6.9Hz), 4.46 (2H, t, J = 6.6Hz), 5.04 (1H, d, J = 5.1Hz), 5.63-5.70 (3H, m), 5.71 (2H, d, J = 55.5Hz), 7.96 (1H, t-like), 8.18 (2H, s), 8.94 (1H, d, J = 8.1Hz), 9.13 (1H, s), 9.65-9.70 (2H, m).
213b	1.31 (3H, d, J = 7.2 Hz), 1.51 (6H, s), 3.33 and 3.63 (2H, ABq, J = 17.7Hz), , 4.33 (2H, q, J = 7.2Hz), 4.87-4.91 (>1H, m), 5.22 (1H, d, J = 4.8 Hz), 5.63 and 5.95 (2H, ABq, J = 14.7Hz), 5.86(1H, d, J = 4.8Hz),7.94 (1H, dd, J = 6.6, 8.4Hz), 8.84 (1H, d, J = 8.4Hz), 8.89 (1H, d, J = 6.6Hz), 8.91 (1H, s).
214b	1.30 (3H, d, J = 6.9 Hz), 2.79 (3H, s), 3.31 and 3.63 (2H, ABq, J = 18Hz), 3.72 (2H, t, J = 6.3 Hz), 4.33 (2H, q, J = 6.9Hz), 4.95 (2H, t, J = 6.3 Hz), 5.22 (1H, d, J = 4.8 Hz), 5.63 and 5.94 (2H, ABq, J = 14.7Hz), 5.85 (1H, d, J = 4.8Hz),7.93 (1H, dd, J = 6.3, 8.4Hz), 8.85 (1H, d, J = 8.4Hz), 8.90 (1H, d, J = 6.3Hz), 8.94 (1H, s).
214c	2.79 (3H, s), 3.29 and 3.63 (2H, ABq, J = 18Hz), 3.71 (2H, t, J = 6.3 Hz), 4.94 (2H, t, J = 6.3 Hz), 5.23 (1H, d, J = 4.8 Hz), 5.63 and 5.92 (2H, ABq, J = 14.7Hz), 5.82 (2H, d, J = 54.6Hz),5.85 (1H, d, J = 4.8Hz), 7.9 (1H, dd, J = 6.3, 8.4Hz), 8.83 (1H, d, J = 8.4Hz), 8.90 (1H, d, J = 6.3Hz), 8.93(1H, s).
215d	2.38-2.48 (2H, m), 3.23 (2H, t, J = 8Hz), 3.29 and 3.63 (2H, ABq, J = 18Hz), 3.41 (2H, t, J = 5 Hz), 4.28 (2H, t, J = 4.8Hz), 4.49-4.85 (ca 6H, m), 5.23 (1H, d, J = 4.8 Hz), 5.62 and 5.88 (2H, ABq, J 15Hz),, 5.86 (1H, d, J = 4.8Hz), 7.89 (1H, dd, J = 6.3, 8.4Hz), 8.80 (1H, d, J = 8.4Hz), 8.86 (1H, d, J = 6 Hz), 8.87 (1H, s).
216d	2.36-2.46 (2H, m), 3.18-3.24 (4H, m), 3.30 and 3.64 (2H, ABq, J = 18Hz), 3.82 (2H, t, J = 5.1Hz), 4.48-4.((ca 6H, m), 5.24 (1H, d, J = 4.8 Hz), 5.63 and 5.89 (2H, ABq, J = 14.7Hz),, 5.86 (1H, d, J = 4.8Hz), 7.89 (1 dd, J = 6.3, 8.1Hz), 8.81 (1H, d, J = 8.1Hz), 8.84 (1H, d, J = 6.3 Hz), 8.87 (1H,s) s).
216b	1.30 (3H, t, J = 7.2Hz), 2.43-2.53 (2H, m), 3.24-3.29 (4H, m), 3.33 and 3.66 (2H, ABq, J = 18.3Hz), 3.88 (2H, t, J = 5.1Hz), 4.29 (2H, q, J = 7.2Hz), 4.68 (2H, t, J = 7.2Hz), 5.26 (1H, d, J = 5.1Hz), 5.67 and 5.92 (2H, ABq, J = 14.7 Hz),), 5.84 (1H, d, J = 5.1Hz), 7.00 (1H, s). 792 (1H, dd, J = 6.6, 7.8Hz), 8.86 (1H, d, J = 7.8Hz), 8.89 (1H, d, J = 6.6Hz), 8.93 (1H, s).

(Table 2 – 2)

No.	^{1}H-NMR (D_2O) δ:
216g	2.38-2.49 (2H, m), 3.19-3.25 (4H, m), 3.31 and 3.64 (2H, ABq, J = 18Hz), 3.84 (2H, t, J = 5.1Hz), 4.65 (2H, t, J = 7.2Hz), 5.25 (1H, d, J = 4.8Hz), 5.69 and 5.93 (2H, ABq, J = 14.7 Hz),), 5.90 (1H, d, J = 4.8Hz), 7.88 (1H, dd, J = 6.3, 8.1Hz), 8.81 (1H, d, J = 8.1Hz), 8.85 (1H, d, J = 6.3Hz), 8.89 (1H, s).
220b	[D6-DMSO]: 1.18 (3H, t, J = 7.2Hz), 2.62 (3H, s), 3.02and 3.54 (2H, ABq, J = 18 Hz), 4.10 (2H, q, J = 7.2 Hz), 5.10 (1H, d, J = 4.8Hz), 5.55 (2H, br s), 5.76 (1H, dd, J = 4.8, 8.4Hz), 7.52 (1H,dd, J = 6.6, 7.8Hz), 8.10 (2H, s), 8.39 (1H, d, J = 7.8Hz), 8.78 (1H, br d, J = 5.1Hz), 9.51 (1H, d, J = 8.4Hz), 12-14 (1H, br).
221b	1.30 (3H, t, J = 6.9Hz), 2.23-2.33 (2H, m), 2.84 (3H, s), 3.15 (2H, t, J = 8.0Hz), 3.24 and 3.61 (2H, ABq, J = 18 Hz), 4.33 (2H, q, J = 6.9Hz), 4.47-4.60 (2H, m), 5.21 (1H, d, J = 5.1 Hz), 5.55 and 5.77 (2H, ABq, J = 14.4Hz), 5.85 (1H, d, J = 5.1Hz), 7.77 (1H, dd, J = 6.2, 7.8 Hz), 8.62 (1H, d, J = 8.1 Hz), 8.68 (1H, d, J = 6.2 Hz).
221c	2.22-2.33 (2H, m), 2.83 (3H, s), 3.15 (2H, t, J = 8.0Hz), 3.26 and 3.63 (2H, ABq, J = 18Hz), 4.54 (2H, t, J = 7.5Hz), 5.25 (1H, d, J = 4.8Hz), 5.60 and 5.75 (2H, ABq, J = 15Hz), 5.82 (2H, d, J = 54.3Hz), 5.88 (1H, d, J = 4.8Hz), 7.77 (1H, dd, J = 6.6, 8.4Hz), 8.61 (1H, d, J = 8.4Hz), 8.68 (1H, d, J = 6.6Hz).
221d	2.22-2.33 (2H, m), 2.84 (3H, s), 3.15 (2H, t, J = 8.0Hz), 3.26 and 3.62 (2H, ABq, J = 18Hz), 4.45-4.87 (ca 6H, m), 5.24 (1H, d, J = 4.8Hz), 5.59 and 5.79 (2H, ABq, J = 14.7Hz), 5.87 (1H, d, J = 4.8Hz), 7.77 (1H, dd, J = 6.3, 8.4Hz), 8.63 (1H, d, J = 8.4Hz), 8.68 (1H, d, J = 6.3Hz).
221a	2.22-2.33 (2H, m), 2.83 (3H, s), 3.14 (2H, t, J = 8.0Hz), 3.26 and 3.62 (2H, ABq, J = 17.7Hz), 4.05 (3H, s), 4.54 (2H, t, J = 7.2Hz), 5.23 (1H, d, J = 4.8Hz), 5.55 and 5.77 (2H, ABq, J = 15 Hz), 5.86 (1H, d, J = 4.8 Hz), 7.77 (1H, dd, J = 6.6, 8.4Hz), 8.62 (1H, d, J = 8.4Hz), 8.68 (1H, d, J = 6.6Hz).
222b	1.30 (3H, t, J = 6.9Hz), 2.25-2.34 (2H, m), 2.73 (3H, s), 2.84 (3H, s), 3.19 (2H, t, J = 8.1Hz), 3.26 and 3.61 (2H, ABq, J = 18Hz), 4.33 (2H, q, J = 6.9Hz), 4.50-4.58 (2H, m), 5.23 (1H, d, J = 4.8 Hz), 5.55 and 5.78 (2H, ABq, J = 15.0Hz), 5.85 (1H, d, J = 4.8Hz), 7.78 (1H, dd, J = 6.6, 8.1Hz), 8.62 (1H, d, J = 8.1Hz), 8.69 (1H, d, J = 6.6Hz).
222c	2.25-2.35 (2H, m), 2.73 (3H, s), 2.83 (3H, s), 3.18 (2H, t, J = 8.1Hz), 3.24 and 3.61 (2H, ABq, J = 18Hz), 4.54 (2H, t, J = 7.5 Hz), 5.24 (1H, d, J = 4.8Hz), 5.55 and 5.77 (2H, ABq, J = 14.4Hz), 5.86 (1H, d, J = 4.8Hz), 5.82 (2H, d, J = 54.3Hz), 7.77 (1H, dd, J = 6.3,7.8Hz), 8.61 (1H, d, J = 7.8Hz), 8.69 (1H, d, J = 6.3Hz).
223c	2.27-2.37 (2H, m), 2.84 (3H, s), 3.14-3.25 (4H, m), 3.26 and 3.63 (2H, ABq, J = 17.7Hz), 3.82 (2H, t, J 5.1Hz), 4.51-4.62 (ca 2H, m), 5.24 (1H, d, J = 4.8 Hz), 5.54 and 5.77 (2H, ABq, J = 14.7Hz), 5.82 (1H, d, = 54.3Hz), 5.87 (1H, d, J = 4.8Hz), 7.77 (1H, dd, J = 6.3, 8.1Hz); 8.62 (1H, d, J = 8.1Hz), 8.69 (1H, d, J 6.3 Hz).

(Table 2 - 3)

No.	^{1}H-NMR (D_2O) δ:
224b	1.30 (3H, t, J=7.2 Hz), 2.79 (3H, s), 2.87 (3H, s), 3.27 and 3.61 (2H, ABq, J=18 Hz), 3.61 (2H, t, J=6.6 Hz), 4.33 (2H, q, J=7.2 Hz), 4.64-4.87 (2H, m), 5.22 (1H, d, J=4.8 Hz), 5.56 and 5.82 (2H, ABq, J=15 Hz), 5.85 (1H, d, J=4.8 Hz), 7.81 (1H, dd, J=6.6, 8.1 Hz), 8.66 (1H, d, J=8.1 Hz), 8.73 (1H, d, J=6.6 Hz)
224c	2.79 (3H, s), 2.86 (3H, s), 3.24 and 3.62 (2H, ABq, J=18 Hz), 3.61 (2H, t, J=6.3 Hz), 4.71-4.85 (2H, m), 5.23 (1H, d, J=4.8 Hz), 5.56 and 5.81 (2H, ABq, J=14.4 Hz), 5.82 (2H, d, J=54.6 Hz), 5.86 (1H, d, J=4.8 Hz), 7.80 (1H, dd, J=6.6, 8.1 Hz), 8.65 (1H, d, J=8.1 Hz), 8.74 (1H, d, J=6.6 Hz)
225c	1.47 (3H, t, J = 7.2Hz), 2.22-2.32 (2H, m), 3.10-3.18 (4H, m), 3.29 and 3.64 (2H, ABq, J = 18Hz), 4.52 -4.61 (2H, m), 5.24 (1H, d, J = 5.1Hz), 5.58 and 5.82 (2H, ABq, J = 14.7Hz), 5.82 (2H, d, J = 54.6Hz), 5.88 (1H, d, J = 4.8Hz), 7.76 (1H, dd, J = 6.6, 8.1Hz), 8.61 (1H, d, J = 8.1Hz), 8.67 (1H, d, J = 6.6Hz).
226b	1.30 (3H, t, J = 7.2Hz), 1.47 (3H, t, J = 7.5Hz), 2.24-2.36 (2H, m), 2.73 (3H, s), 3.14 (2H, q, J = 7.5Hz), 3.18 (2H, m), 3.35 and 3.64 (2H, ABq, J = 18 Hz), 4.33 (2H, q, J = 7.2Hz), 4.55 (2H, d, J = 8.1Hz), 5.24 (1H, d, J = 5.1 Hz), 5.62 and 5.90 (2H, ABq, J = 14.7Hz), 5.88 (1H, d, J = 5.1Hz), 7.77 (1H, dd, J = 6.6, 8.4Hz), 8.63 (1H, d, J = 8.4 Hz), 8.68 (1H, d, J = 6.6 Hz).
226c	1.47 (3H, t, J = 7.5Hz), 2.25-2.32 (2H, m), 2.73 (3H, s), 3.11-3.22 (4H, m), 3.30 and 3.63 (2H, ABq, J = 18.3Hz), 4.54 (2H, t, J = 7.2 Hz), 5.24 (1H, d, J = 5.1Hz), 5.58 and 5.86 (2H, ABq, J = 14.7Hz), 5.86 (1H, d, J = 5.1Hz), 5.82 (2H, d, J = 54.6Hz), 7.76 (1H, dd, J = 6.6 ,8.1Hz), 8.61 (1H, d, J = 8.1Hz), 8.68 (1H, d, J = 6.6Hz).
227c	[D6-DMSO]: 2.36 (center, 2H, m), 2.57 (3H, s), 3.13 (center, 2H, m), 3.17 and 3.59 (2H, ABq, J = 18Hz), 4.81 (center, 2H, m), 5.09 (1H, d, J = 4.8Hz), 5.51-5.78 (3H, m), 5.71 (2H, d, J = 53.1Hz), 8.05 (1H, d, J = 6.6Hz), 8.26 (2H, br s), 9.33 (1H, d, J = 7.8Hz), 9.65-9.68 (2H,m).
231b	1.20 (3H, t, J = 7.2Hz), 2.97 and 3.52 (2H, ABq, J = 18.3 Hz), 4.12 (2H, q, J = 7.2 Hz), 5.15 (1H, d, J = 4.8Hz), 5.18 (2H, m), 5.81 (1H, dd, J = 4.8, 8.4Hz), 6.95 (1H, t, J = 7.2Hz), 7.26 (1H, d, J = 7.2Hz), 7.85 (1H, d, J = 6.6Hz), 8.10 (2H, br s), 9.57 (1H, d, J = 8.4Hz), 11.10(1H, s).
232b	1.20 (3H, t, J = 7.2Hz), 3.32 and 3.47 (2H, ABq, J = 18 Hz), 4.13 (2H, q, J = 7.2 Hz), 5.13 (1H, d, J = 5.1 Hz), 5.30 and 5.52 (2H, ABq, J = 15Hz), 5.87 (1H, dd, J = 5.1, 8.4Hz), 7.23 (1H, t, J = 7.5Hz), 7.80 (1H, d, J = 7.8Hz), 8.09 (1H, d, J = 6.6Hz), 8.14 (2H, s), 8.34 (2H, s), 9.56 (1H, d, J = 8.4Hz), 12.37(1H, br s).
233b	1.22 (3H, t, J = 7.2Hz), 2.19 (center, 2H, m), 2.86 (center, 2H, m), 3.16 and 3.30 (2H, ABq, J = 17 Hz), 3.00-3.15 (3H, m), 4.13 (2H, q, J = 7.2 Hz), 5.00 (1H, d, J = 4.8 Hz), 5.36 (1H, J = 13.2Hz), 5.83 (1H, dd, J = 4.8, 8.4Hz), 6.17(1H, br m), 7.65 (1H, t, J = 7.2Hz), 8.15 (2H, s), 8.22 (2H, br s), 8.54 (1H, d, J = 8.4Hz), 8.77 (1H, d, J = 5.7Hz), 9.52 (1H d, J = 8.4Hz).

(Table2－4)

No.	^{1}H-NMR (D6-DMSO) δ :
234b	1.22 (3H, t, J = 7.2Hz), 2.22 (center, 2H, m), 2.85 (center, 2H, m), 3.00 and 3.37 (2H, ABq, J = 17 Hz), 3.00-3.16 (3H, m), 3.92 (3H, s), 4.15 (2H, q, J = 7.2 Hz), 4.89(1H, d, J = 5.1 Hz), 5.24 and 6.63 (2H, ABq, J = 14Hz), 5.83 (1H, dd, J = 5.1, 8.4Hz), 7.83 (1H, dd, J = 6.3, 8.3Hz), 8.16 (2H, s), 8.50 (2H, br s), 8.32 (1H, d, J = 8.3Hz), 8.98 (1H, d, J = 6.3Hz), 9.48 (1H d, J = 8.4Hz).
234c	2.21 (center, 2H, m), 2.86 (center, 1H, m), 3.08 and 3.37 (2H, ABq, J = 17 Hz), 3.02-3.19 (3H, m), 3.93 (3H, s), 4.94 (1H, d, J = 4.8Hz), 5.32 and 6.52 (2H, ABq, J = 14Hz), 5.76 (2H, d, J = 54Hz), 5.85 (1H, m), 7.85 (1H, dd, J = 6, 8.1Hz),), 8.25 (2H, s), 8.46 (2H, br s), 8.83 (1H, d, J = 8.1Hz), 8.98 (1H, d, J = 6 Hz), 9.71 (1H, d, J = 8.1Hz).
240b	1.16 (3H, t, J = 7.2Hz), 3.01 and 3.56 (2H, ABq, J = 17.7Hz), 3.80 (2H, t, J = 4.5Hz), 4.08 (2H, q, J 7.2Hz), 4.55 (2H, m), 5.02 (1H, d, 5.1Hz), 5.61 and 5.70 (2H, ABq, J = 13.5Hz), 5.69 (1H, dd, J = 5.1, 8.4Hz 7.91(1H, dd, J = 6.0, 8.1Hz), 8.15 (2H, br s), 8.91(1H, d, J = 8.1 Hz), 9.05 (1H, s), 9.45 (1H, d, J = 8.4Hz 9.51 (1H, d, J = 6.0 Hz).
240c	2.99 and 3.56 (2H, ABq, J = 17.4Hz), 3.82 (2H, t, J = 4.5Hz), 4.55 (2H, t, J = 4.5Hz), 5.04 (1H, d, 5.1Hz 5.67 (3H, m), 5.71 (1H, d, J = 55.2Hz), 7.94(1H, dd, J = 6.0, 8.1Hz), 8.20 (2H, br s), 8.91(1H, d, J = 8.1 Hz 9.05 (1H, s), 9.63 (1H, d, J = 6.0Hz), 9.68 (1H, d, J = 8.1 Hz).
241b	[D_2O Addition]: 1.16 (3H, t, J = 7.2Hz), 3.12 and 3.50 (2H, ABq, J = 17.1Hz), 4.10 (2H, q, J = 7.2Hz), 5.0 (1H, d, 4.8Hz), 5.64 and 5.76 (2H, ABq, J = 14.4Hz), 5.69 (1H, d, J = 4.8Hz), 8.02 (1H, m), 8.10(1H, d, = 59.1 Hz), 8.92 (1H, d, J = 7.8 Hz), 9.34 (1H, s), 9.50 (1H, d, J = 6.3Hz).
241c	[D_2O Addition]: 3.11 and 3.51 (2H, ABq, J = 17.7Hz), 5.02(1H, d, J = 4.8Hz), 5.63 and 5.75 (2H, ABq, =15Hz), 5.69 (1H, d, J = 4.8Hz), 5.71 (2H, d, J = 55.5Hz), 8.02 (1H, dd, J =6.3, 7.2Hz), 8.09 (1H, d, J = 58.8 Hz 8.92 (1H, d, J = 7.2 Hz), 9.34 (1H, s), 9.50 (1H, d, J = 6.3Hz).
241g	[D_2O Addition]: 3.13 and 3.52 (2H, ABq, J = 18.3Hz), 5.03 (1H, d, J = 5.1Hz) 5.67 and 5.77 (2H, ABq, J = 13.5Hz), 5.71 (1H, d, J = 5.1Hz), 8.06 (1H, dd, J = 6.1, 8.3 ヘルツ), 8.16 (1H, d, J = 58.5Hz), 8.96 (1H, d, J = 8.3 Hz), 9.40 (1H, s), 9.60 (1H, d, J = 6.1Hz).

(Table2－5)

No.	^{1}H-NMR (DG-DMSO) δ :
242b	1.18 (3H, t, J = 7.2 Hz), 3.03 and 3.53 (2H, ABq, J = 17.7Hz), 4.11 (2H, q, J = 7.2 Hz), 5.02 (1H, d, 4.5Hz), 5.13 and 5.19 (2H, ABq, J = 14Hz), 5.29-5.31 (1H, m), 5.35 (1H; d, J = 1.2Hz), 5.66-5.70 (3H, m), 6.03-6.19 (1H, m), 7.95 (1H, dd, J = 6.0, 8.4 Hz), 8.11 (2H, br s), 8.83 (1H, d, J = 7.8 Hz), 9.09 (1H, s), 9.44 (1H, d, J = 8.4 Hz), 9.68 (1H, d, J = 6.0Hz).
242c	3.02 and 3.54 (2H, ABq, J = 17.4Hz), 5.04 (1H, d, 5.1Hz), 5.14 and 5.19 (2H, ABq, J = 14Hz), 5.30 (1H, d, J = 2.7Hz), 5.35 (1H, s), 5.67 (3H, m), 5.71 (2H, d, J = 55.8 Hz), 6.00-6.20 (1H, m), 7.95 (1H, dd-like), 8.19 (2H, br s), 8.83 (1H, d, J = 7.8 Hz), 9.09 (1H, s), 9.67 (1H, d, J = 8.1 Hz), 9.68 (1H, d, J = 5.4Hz).
243b	1.18 (3H, t, J = 7.2 Hz), 3.07 and 3.53 (2H, ABq, J = 17.7Hz), 3.32 (3H, s), 4.10 (2H, q, J = 7.2 Hz), 5.02 (1H, d, 5.1Hz), 5.64-5.71 (3H, m), 5.85 (2H, s), 8.00 (1H, dd, J =6,3 8.1Hz), 8.11(2H, br s), 8.92(1H, d, J = 8.1Hz), 9.25 (1H, s), 9.45 (1H, d, J = 8.7 Hz), 9.70(1H, d, J = 6.3Hz).
244b	1.18 (3H, t, J = 7.2 Hz), 2.33-2.42 (2H, m), 3.00 and 3.52 (2H, ABq, J = 17.4Hz), 3.69 (2H, t, J = 6.6 Hz), 4.07 (2H, q, J = 7.2 Hz), 4.62 (2H, t, J = 7.2 Hz), 5.02 (1H, d, J = 4.8 Hz), 5.67-5.70 (3H, m), 7.97 (1H, dd, J = 6.6, 8.1 Hz), 8.12 (2H, br s), 8.94 (1H, d, J = 8.1 Hz), 9.12 (1H, s), 9.45 (1H, d, J = 9.0 Hz), 9.70 (1H, d, J = 6.6 Hz).
245b	0.68 (2H, d, J = 6Hz), 0.88 (2H, br s), 1.18 (3H, t, J = 7.2 Hz), 2.31 (center, 2H, m), 2.61 (1H, m), 3.03 (2H, t, J = 7.2 Hz), 3.08 and 3.47 (2H, ABq, J = 16 Hz), 4.10 (2H, q, J = 7.2 Hz), 4.64 (2H, t, J = 7.2 Hz), 5.04 (1H, d, J = 4.8 Hz), 5.56 and 5.74 (2H, ABq, J = 14.4 Hz),), 5.75 (1H, d, J = 4.8 Hz), 7.87 (1H; dd, J = 6.2, 8.1 Hz), 8.12 (2H, br s), 9.00 (1H, d, J = 8.4 Hz), 9.16 (1H, s), 9.26 (1H, d, J = 6.2 Hz), 9.46 (1H, d, J = 8.1 Hz).
246b	1.18 (3H, t, J = 7.2 Hz), 2.92 and 3.50 (2H, ABq, J = 18 Hz), 2.95 (3H, s), 4.10 (2H, q, J = 7.2 Hz), 4.21 (3H, s), 5.01 (1H, d, J = 4.8 Hz), 5.58 (2H, br s), 5.67 (1H, dd, J = 4.8, 8.7 Hz), 7.71 (1H, d, J = 6.9 Hz), 8.13 (2H, br s), 8.91 (1H, s), 9.45 (1H, d, J = 6.9 Hz), 9.49 (1H, d, J = 8.7 Hz).

(Table2－6)

No.	^{1}H-NMR (D_2O) δ:
250b	[D6-DMSO]: 1.18 (3H, t, J = 7.2 Hz), 3.10 and 3.45 (2H, ABq, J = 17.7Hz), 4.11 (2H, q, J = 7.2Hz), 4.60-4.68 (4H, m), 5.07 (1H, d, J = 4.8Hz), 5.63 (1H, J = 13.5 Hz), 5.75 (1H, dd, J = 4.8, 8.4Hz), 5.85- 5.89 (2H, m), 8.01 (1H, dd, J = 6.3, 8.1Hz), 8.15 (2H, s), 9.19 (1H, d, J = 8.1Hz), 9.41 (1H, d, J = 6.3 Hz), 9.49 (1H, d, J = 8.4 Hz), 9.56 (1H, s).
250c	3.09 and 3.46 (2H, ABq, J = 18Hz), 4.60-4.63 (4H, m), 5.04 (1H, d, J = 5.1Hz), 5.66 (2H, d, J = 53 Hz), 5.62- 5.87 (4H, m), 7.95 (1H, t-like), 8.18 (2H, s), 9.12 (1H, d, J = 8.1Hz), 9.30 (1H, d, J = 9 Hz), 9.51 (1H, s), 9.68 (1H, d, J = 8.1 Hz),
251b	[D6-DMSO]: 1.17 (3H, t, J = 6.6Hz), 2.69 (center, 2H, m), 3.15 and 3.47 (2H, ABq, J = 18Hz), 3.47-3.81 (4H, m), 4.10 (2H, q, J = 6.6Hz), 5.04 (1H, d, J = 5.1Hz), 5.31 and 5.88 (2H, ABq, J = 13.5Hz), 5.60(1H, m), 5.80 (1H, dd, J = 5.1, 8.4Hz), 7.94 (1H, dd, J = 7.2, 7.5Hz), 8.12 (2H, s), 9.03-9.05 (2H, m), c9.50 (1H, d, J = 8.4Hz),
252b	[65/35 mixture] 1.30 (3H, t, J = 7.2Hz), 2.67-2.98 (2H, m), 3.31 and 3.62 (2H, ABq, J = 18Hz), 3.83-3.90 (1H, m), 4.00-4.17 (1H, m), 4.26-4.38 (2H, m), 4.33 (2H, q, J = 7.2Hz), 5.22 (1H, d, J = 4.8Hz), 5.61 and 5.93 (2H, ABq, J = 14.4Hz), 5.85 (1H, d, J = 4.8Hz), 7.91 (1H, dd, J = 6.3, 8.1Hz), 8.13 and 8.15 (ca0.65H and 0.35H, each s), 8.84 (1H, d, J = 8.1Hz), 8.87 (1H, d, J = 6.3 Hz), 8.90 and 8.95 (ca 0.65H and 0.35H, each s).
253b	[55/45 mixture] 1.30 (3H, t, J = 7.2Hz), 2.36 and 2.40 (1.65H and 1.35H, each s), 2.67-2.98 (2H, m), 3.35 and 3.66 (2H, ABq, J = 18Hz), 3.82-3.89 (1H, m), 3.99-4.08 (1H, m), 4.21-4.51 (2H, m), 4.32 (2H, q, J = 7.2Hz), 5.25 (1H, d, J = 4.8Hz), 5.62-5.74 (1H, m), 5.72 and 5.99 (2H, ABq, J = 14.7Hz), 5.87 (1H, d, J = 4.8Hz), 7.92 (1H, dd, J = 6.3, 8.1Hz), 8.86 (1H, d, J = 8.1Hz), 8.92 (1H, d, J = 6.3 Hz), 8.93 and 8.95 (ca0.55H and 0.45H, each s).
254b	1.30 (3H, t, J = 7.2 Hz), 2.74-2.84 (1H, m), 3.01 (center, 1H, m), 3.11 (3H, s), 3.31 and 3.63 (2H, ABq, J = 17.7Hz), 3.35-4.25 (4H, m), 4.33 (2H, q, J = 7.2Hz), 5.22 (1H, d, J = 4.8Hz), 5.61 and 5.94 (2H, ABq, J = 14.7Hz), 5.76 (center, 1H, m), 5.85 (1H, d, J = 4.8Hz), 7.92 (1H, dd, J = 6.3, 8.1Hz), 8.82 (1H, d, J = 8.1Hz), 8.88 (1H, d, J = 6.3 Hz), 9.05 (1H, s).
255c	[DG-DMSO]: 2.20 (2H, br s), 3.15 and 3.45 (2H, ABq, J = 17.7Hz), 3.28 (3H, s), 3.56 (2H, br s), 4.10 (2H, br s), 5.05 (1H, d, J = 4.8Hz), 5.32 and 5.33 (2H, ABq, J = 14.4Hz), 5.74 (2H, d, J = 55.2 Hz), 5.73 (1H, dd, J = 4.8,8.1Hz), 7.21 (1H, t, J = 6.9Hz), 7.90 (1H, d, J = 7.5Hz), 8.22 (2H, br s), , 8.61 (1H, d, J = 6Hz), 9.71 (1H, d, J = 8.1 Hz).

(Table 3 – 1)

No.	IR (KBr) cm^{-1} (Data in " ( ) " is of 4-ester of quaternary ammonium salt ???)
211b	3406, 2979,1772, 1614, 1527, 1389, 1117, 1037, 619. ($CHCl_3$: 3260, 3220, 1773, br1704, 1633, 1611, 1240, 1151, 1037.)
211c	3388, 1772, 1672, 1612, 1527, 1396, 1117, 619. ($CHCl_3$: br 3218, 1771, br1713, 1634, 1611, 1243, 1154.)
212c	3405, 2975, 1780, 1675, 1616,, 1529, 1487, 1461, 1394, 1153, 1062, 991, 862, 760 .
213b	3405, 1774, 1672, 1631, 1525, 1385, 1117, 1037, 611. (Nujol : 3213, 1788, br1713, 1633, 1612, 1248, 1157, 1038, .)
214b	3398, 1772, 1668, 1610, 1527,1389, 1234, 1117, 1038, 619. (Nujol : 3210, 1788, 1716, 1686, 1635, 1612, 1247, 1174, 1155, 1038.)
214c	3425, 1772, 1672, 1612, 1525, 1394 ,1120, 1081, 619. (Nujol : 3210, 1788, 1716, 1686, 1635, 1612, 1247, 1174, 1155, 1038.)
215d	3409, 1774, 1671, 1633, 1527, 1389, 1230, 1151, 1063, 1018, 759, 625, 581.
216d	3394, 1772, 1672, 1635, 1612, 1527, 1390, 1120, 1065, 619. ($CHCl_3$: 3401, 3223, br1774, 1718, 1684, 1635, 1612, 1247, 1174, 1155, 1062.)
216b	3374, 1776, 1664, br 1635, 1535, 1464, 1385, 1115, 1034, 758, 619. ($CHCl_3$: 3406, 1792, 1722, 1681, 1635, 1612, 1228, 1155, 1037.)
216g	3384, 1772, 1670, br 1612, 1527, 1464, 1389, 1066, 1018, 760.
220b	3423, 1756, 1666, 1647, 1603, 1539, 1458, 1396, 1038,762.
221b	3408, 1770, 1668, 1616, 1525, 1463, 1398, 1119, 1037, 619. (Nujol: 3267, 3221, 1772, 1714, 1686, 1637, 1612, 1250, 1159, 1109, 1037.)

(Table 3 – 2)

No.	IR (KBr) cm $^{-1}$
221c	Nujol : 3278, 3116, 3045, 1772, 1714, 1685, 1641, 1277, 1234, 1090. (Nujol: 3267, 3217, 1770, 1712, 1691, 1637, 1614, 1250, 1174, 1157, 1120, 1005.)
221d	3408, 3174, 3030, 1778, 1674, 1635, 1525, 1463, 1400, 1113, 1065, 619.
221a	3409, 3035, 1772, 1670, 1616, 1463, 1398, 1118, 1039, 619. ($CHCl_3$: 3406, 3213, 1770, 1713, 1637, 1612, 1247, 1174, 1155, 1039.)
222b	3413, 1774, 1672, 1635, 1525, 1464, 1398, 1117, 1039, 619.
222c	3406, 1774, 1674, 1616, 1527, 1463, 1398, 1119, 1083, 619.
223c	3406, 1774, 1673, 1614, 1527, 1463, 1400, 1117, 1082, 619. (Nujol: 3400,3214,1789,1714,1682,1614,1250,1155,860.)
224b	Nujol:3309, 1763, br1680, 1610, 1039. (Nujol: 3434, 3219, 1784, 1716, 1686, 1637, 1612, 1585, 1248, 1157, 1038.)
224c	Nujol:3310, 1768, 1672, 1603, 1057. (Nujol: 3433, 3201, 1768, 1732, 1712, 1689, 1639, 1614, 1248, 1155, 1120, 1001.)
225c	3400, 1774, 1676, 1616, ,1527, 1466, 1400, 1113, 1072, 617.
226b	3406, 3184, 2983, 1782, 1674, 1637, 1525, 1467, 1221, 1153, 1110, 1039, 617, 588. (Nujol: 3430, 3271, 3213, 1770, 1714, 1684, 1639, 1614, 1248, 1157, 1035,.)
226c	3409, 3030, 2810, 1776, 1676, 1635, 1616, ,1527, 1465, 1402, 1119, 1080, 619 (Nujol: 3428, 3265, 3201, 1767, 1730, 1711, 1689, 1639, 1614, 1248, 1155, 1120, 1057.)

(Table 3 – 3)

No.	IR (KBr) cm^{-1}
227c	3401, 1770, 1674, 1523, 1475, 1265, 1203, 1132, 721.
231b	3412, 1771, 1655, 1625, 1522, 1399, 1358, 1298, 1153, 1038, 758.
232b	3340, 3190, 1776, 1661, 1567, 1524, 1490, 1402, 1311, 1217, 1162, 1035, 760.
233b	3398, 3171, 3023, 1772, 1670, br1613, 1526, 1461, 1401, 1356, 1037, 760.
234b	3398, 3034, 1767, 1670, 1614, 1525, 1475, 1394,1356, 1319, 1148, 1037, 758.
234c	3398, 3023, 1774, 1676, 1616, 1523, 1475, 1396, 1321, 1139, 1078, 1060, 991, 758.
240b	3399, 1774, 1670, br 1613, 1527, 1386, 1292, 1234, 1038, 759.
240c	3422, 1773, 1672, br 1614, 1525, 1389, 1292, 1235, 1069, 991, 760.
241b	3396, 1774, 1669, 1611, 1528,1458, 1411, 1320, 1083, 1038, 823.
241c	3414, 1774, 1674, 1613, 1527, 1459, 1413, 1321, 1227, 1081, 823.
241g	3414, 1773, 1670, 1612, 1525, 1459, 1413, 1394, 1321, 1242 1078, 823.
242b	3400, 1775, 1670 br 1613, 1528, 1383, 1290, 1234, 1038, 783.

(Table 3 – 4)

No.	IR (KBr) cm $^{-1}$
242c	3386, 1776, 1674, br 1612, 1528, 1382, 1290, 1234, 1076, 784, 760,
243b	3400, 1776 1671, br 1614, 1527, 1389, 1296, 1231, 1104, 1038, 757.
244b	3396, 1774, 1672, br 1614, 1527, 1462, 1387, 1234, 1037, 760.
245b	3398, 1774, 1670, 1635, 1612, 1527, 1387, 1236, 1065, 756.
246b	3398, 1764, 1680, br 1616, 1533, 1391, 1358, 1239, 1152, 1038, 631.
250b	3399, 1770, 1669 ,br 1611, 1525,1484, 1390, 1353, 1146, 1037, 759.
250c	3410, 1772, 1674, 1612, 1525, 1462, 1394, 1352, 1138, 1063, 987, 760.
251b	3412, 1777, 1677, 1636, 1528, 1463, 1406, 1202, 1132, 1039, 800, 722.
252b	3392, 1772, 1707, br 1670, 1606, 1525, 1462, 1389, 1348, 1036, 758.
253b	3383, 1772, 1672, br 1630, 1462, 1389, 1360, 1038, 758.
254b	3415, 1770, 1668, br 1610, 1527, 1462, 1392, 1354, 1038, 760.
255c	3400, 1770,1654,1616, 1595, 1524, 1417, 1321, 1144, 1084, 758.

(Table 4-1)

No.	Elementary Anallysis	Calculated value (%)						Measured value (%)					
		C	H	N	S	F	Cl	C	H	N	S	F	Cl
211b	C23H26N10O5S2·0.5H2SO4·6H2O	37.14	5.29	18.83	10.78			37.06	5.10	18.69	10.79		
211c	C22H23N10O5S2F·0.5H2SO4·5.5H2O	35.77	4.78	18.96	10.85	2.57		35.63	4.66	18.97	11.08	2.45	
212c	C28H33N10O7S2F·0.5H2SO4·8H2O	44.32	5.18	18.46	8.45	2.50		44.42	5.13	18.67	8.30	2.35	
213b	C24H28N10O5S2·1.0H2SO4·4.5H2O	36.97	5.04	17.96	12.34			36.84	4.85	18.10	12.51		
214b	C23H26N10O5S2·0.5H2SO4·4H2O	39.03	4.98	19.79	11.33			38.95	4.79	19.68	11.14		
214c	C22H23N10O5S2F·0.5H2SO4·5H2O	36.21	4.70	19.19	10.99	2.60		36.17	4.42	19.28	10.72	2.76	
215d	C25H29N10O3S3F·0.3H2SO4·5H2O	35.40	4.71	16.51	12.48	2.24		35.60	4.71	16.48	12.36	2.37	
216d	C25H29N10O6S2F·0.7H2SO4·2H2O·0.33iPrOH	40.41	4.83	18.12	11.20	2.46		40.36	4.70	18.05	11.47	2.50	
216b	C26H31N9O6S2·0.85H2SO4·2.5H2O	41.19	5.01	16.63	12.05			41.33	4.91	16.75	11.97		
216g	C23H26N10O6S2·1.8HCl·4.2H2O	37.13	4.90	18.83	8.62		8.58	37.00	4.93	19.11	8.59		8.52
220b	C21H21N9O5S2·4H2O	40.97	4.75	20.48	10.42			41.09	4.77	20.62	10.62		
221b	C24H28N10O5S2·0.5H2SO4·5.5H2O	38.50	5.38	18.71	10.71			38.29	5.18	18.78	10.77		
221c	C23H25N10O5S2F·1.0H2SO4·8H2O	32.62	5.12	16.54	11.36	2.24		32.72	4.93	16.58	11.51	2.22	
221d	C24H27N10O5S2F·0.8H2SO4·2H2O	39.33	4.46	19.11	12.25	2.59		39.33	4.33	18.96	12.42	2.48	
221a	C23H26N10O5S2·0.5H2SO4·4.2H2O·0.2iPrOH	39.24	5.02	19.39			11.10	39.23	5.03	19.21			11.38

* FAB+-Mass 215d 9221: [M+1]+729, 216d 9197: [M+1]+649

(Table4--2)

No.	Elementary Anallysis	Calculated value %)						Measured value (%)					
		C	H	N	S	F	Cl	C	H	N	S	F	Cl
222b	C25H30N10O5S2 0.6H2SO4 ·5.5H2O	38.47	5.47	17.95	11.01			38.25	5.08	18.21	11.01		
222c	C24H27N10O5S2F·0.5H2SO4 ·0.8H2O	38.22	5.03	18.57	10.63	2.52		38.27	4.80	18.73	10.54	2.56	
223c	C25H29N10O6S2F·0.7H2SO4 ·7H2O	35.60	5.31	16.61	10.27	2.25		35.59	5.17	16.79	10.22	2.54	
224b	C24H28N10O5S2·0.5H2SO4·5.8H2O	38.22	5.43	18.57	10.63			37.93	5.19	18.90	10.72		
224c	C23H25N10O5S2F·0.65H2SO4·6.4H2O	39.54	4.47	20.05	11.47	2.72		39.62	4.45	20.25	11.29	2.68	
225c	C24H27N10O5S2F·0.65H2SO4·6.4H2O	36.14	5.19	17.56	10.65	2.38		36.09	5.11	17.75	10.70	2.24	
226b	C26H32N10O5S2 1.4H2SO4·6H2O	35.73	5.40	16.02	12.47			35.43	5.11	16.11	12.55		
226c	C25H29N10O5S2F 0.8H2SO4·5.6H2O	36.98	5.19	17.25	11.06	2.34		36.97	4.87	17.33	10.76	2.40	
227c	C24H24N10O5S2F4·0.8CF3CO2H·0.8 HCl· 4.5H2O	35.18	3.99	16.02	7.34	13.91	3.24	35.22	3.64	15.83	7.34	14.07	3.33
231b	C20H19N9O6S2··3.1 H2O	40.06	4.20	21.02	10.70			39.85	4.29	20.99	10.66		
232b	C20H20N10O5S2·1.3 HC1·3 H2O	37.18	4.26	21.68		9.93	7.13	37.46	4.37	21.30		9.62	6.85
233b	C23H26N10O5S2·1.3 HCl ·4.4H2O	38.73	5.10	19.64	8.99		6.46	38.96	5.05	19.65	8.69		6.40
234b	C24H28N10O5S2·1.3 HCl ·5.5H2O	38.58	5.44	18.75	8.58		6.17	38.84	5.51	18.97	8.35		6.28
234c	C23H25N10O5S2F·1.5 HCl ·4.8 H2O	37.04	4.88	18.78	8.60	2.55	7.13	37.31	4.93	18.79	8.43	2.16	7.02
240b	C22H23N9O6S2·3 H2O	42.10	4.66	20.08	10.22			41.89	4.61	20.20	10.26		
240c	C21H20N9O6S2F·3.3 H2O	39.60	4.21	19.79	10.07	2.98		39.59	4.20	20.14	10.17	2.82	
241b	C21H19N9O5S2F2·2.6 H2O	40.21	3.89	20.12	10.24	6.07		40.34	4.05	20.18	10.12	5.89	
241c	C20H16N9O5S2F3·2.2 H2O	38.55	3.30	20.22	10.29	9.15		38.51	3.53	20.50	9.98	9.34	

* LSIMS 231b 9991: [M + 1]+ 546

(Table 4 – 3)

No.	Elementary Anallysis	Calculated value (%)						Measured value (%)					
		C	H	N	S	F	Cl	C	H	N	S	F	Cl
241g	C19H15N9O5S2F2·3 H2O	37.69	3.50	20.82	10.59	6.27		37.89	3.73	20.00	10.79	6.29	
242b	C23H23N9O5S2·3 H2O	44.29	4.69	20.21	10.28			44.23	4.74	20.34	10.01		
242c	C22H20N9O5S2F·1.5 H2O	44.00	3.86	20.99	10.68	3.16		44.25	4.14	20.96	10.64	2.82	
243b	C22H23N9O6S2·3.2 H2O	41.86	4.69	19.97	10.16			41.78	4.59	20.14	10.06		
244b	C23H24N9O5S2Cl·4 H2O	40.74	4.76	18.59	9.46		5.23	40.90	4.85	18.34	9.33		5.06
245b	C26H30N10O5S2·1.2 HCl ·5 H2O	41.06	5.46	18.42	8.43		5.59	41.11	5.47	18.47	8.28		5.79
246b	C22H23N9O5S2·4.6 H2O	41.26	5.07	19.68	10.01			41.44	5.11	19.80	9.74		
250b	C23H24N10O5S2·1.25HCl ·4.5H2O	38.84	4.85	19.69	9.02		6.23	39.08	4.77	19.84	8.67		6.15
250c	22H21N10O5S2F·1.07HCl ·5H2O	36.82	4.50	19.52	8.94	2.65	5.29	36.82	4.36	19.52	8.66	2.60	5.00
251b	C24H26N10O5S2·1.55HCl ·5.5H2O	35.33	4.02	14.11	6.46	14.93		35.38	3.81	14.08	6.45	14.77	
252b	C25H27N11O5S2·2.6 CF3CO2H ·5.5 H2O	39.54	5.07	20.29	8.44		5.60	39.70	5.05	20.17	8.05		5.67
253b	C26H29N11O5S2·1.23HCl ·5.5H2O	39.85	5.30	19.66	8.18		5.57	39.74	5.29	19.80	8.09		5.44
254b	C25H28N10O5S2·1.3HCl ·5.5H2O	39.55	5.35	18.45	8.45		6.07	39.61	5.25	18.43	8.22		6.10
255c	C23H23N10O5S2·1.3HCl ·5.5H2O	38.62	4.62	19.58	9.41	2.66	2.97	38.73	4.38	19.17	9.17	2.38	2.92

* LSIMS 252b 9156 : [M + 1]+ 626, FAB-Mass 255c 204-9211 : [M + 1]+ 603, [M + Na]+ 625.

Experiment

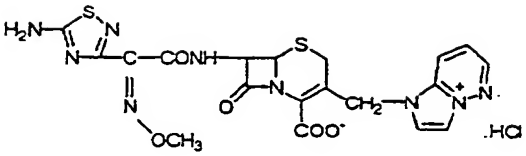
[0220] The minimal inhibitory concentration (MIC) of compound (I) against various bacteria was determined by an agar dilution method. The result is shown in Table 5. As reference compounds, used were cefozopran hydrochloride (CZOP) described in JP(A) Kokai H03-47189, cefoselis sulfate (CFSL) described in JP(A) Kokai H07-196665 and WO97/41128, compound A of which 3-side chain is a type of imidazo[4,5-c]pyridiniummethyl, and vancomycin. In the table, "Ex5-3" , for example, represents the end compound of the present invention obtained in Example 5-3, and the others are similarly expressed.

(Table 5)

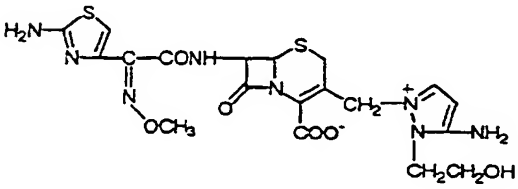
MIC(ug/ml)		Ex5-3	Ex6-2	Ex6-3	Ex4-1	Ex5-2	CZOP	CFSL	A	VCM
G(+)	S.aureus SMITH	0.78	1.56	0.78	0.78	0.78	0.78	0.78	0.78	0.78
	S.aureus SR14	0.78	1.56	0.78	1.56	0.78	0.78	0.78	3.13	0.78
	S.aureus SR3626	3.13	3.13	6.25	3.13	3.13	50	25	25	3.13
	S.aureus SR3637	3.13	3.13	6.25	6.25	3.13	50	25	25	3.13
	S.pneumoniae Type1	0.025	0.025	0.025	0.025	0.025	0.05	0.013	0.0125	0.39
	S.pneumoniae SR16675	0.78	0.78	0.78	0.39	0.78	0.78	0.39	0.39	0.2
	S.mitis SR15376	0.2	0.1	0.2	0.1	0.2	0.2	NT	0.1	0.39
	E.faecalis SR1004	100	50	50	50	50	25	>100	50	
G(-)	E.coli NIH JC-2	0.1	0.39	0.2	0.2	0.39	0.05	0.05	0.05	
	E.coli SR5028	1.56	3.13	1.56	3.13	3.13	0.78	0.78	1.56	
	P.vulgaris CN-329	0.39	0.78	0.39	0.78	0.78	0.2	0.025	0.1	
	E.cloacae ATCC 13047	0.39	0.78	0.78	0.78	0.78	0.2	0.2	0.48	
	E.cloacae SR4321	12.5	25	12.5	25	25	6.25	12.5	12.5	
	S.marcescens ATCC 13880	0.1	0.39	0.2	0.2	0.39	0.1	0.1	0.1	
	P.aeruginosa SR24	1.56	1.56	3.13	0.78	0.78	0.78	3.13	0.78	
	P.aeruginosae SR5393	6.25	6.25	6.25	3.13	3.13	1.56	6.25	3.13	
ED_{50}(mg/kg) mouse/S.aureus SR3637		5.66	7.92	6.43	11.3			37.1		5.66

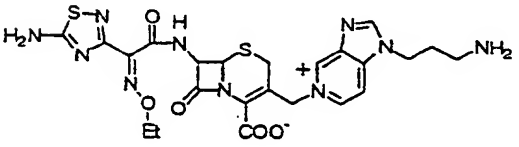
(Reference)

[0221]

CZOP → 

VCM → vancomycin

CFSL → 

A → 

[0222] The result shows that the present compound (I) possesses potent antibacterial activities against various bacteria including MRSA (e.g., S.aureus SR3626 and S.aureus SR3637).

Preparation 1

[0223] Compound 37c obtained in Example 6-3(2) is lyophilized to give an injection.

Preparation 2

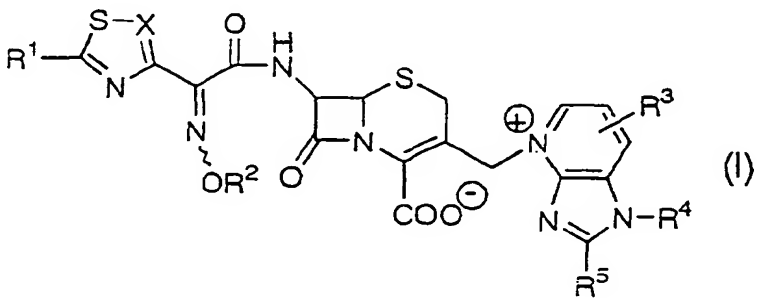
[0224] Powder of compound 108c obtained in Example 29(2) is filled to give an injection.

Industrial Applicability

[0225] The compounds of the present invention are useful as antibacterial agents. The present invention further provides intermediates thereof,

Claims

1. A compound of the formula(I):



(I)

wherein,

X is N or CY and Y is H or halogen;
R^1 is amino or protected amino;
R^2 is hydrogen, optionally substituted lower alkyl or optionally substituted cycloalkyl;
R^3 is hydrogen, hydroxy, halogen, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted lower alkylthio or optionally substituted amino;
R^4 is hydrogen, hydroxy, optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted cycloalkyl, optionally substituted cycloalkyl(lower)alkyl or an optionally substituted N-containing heterocyclic group;
R^5 is hydrogen, amino, optionally substituted lower alkyl, optionally substituted lower alkoxy or optionally substituted lower alkylthio, or R^4 and
R^5 taken together may form lower alkylene in which an optional hetero atom(s) intervene; and
a wavy line means syn- or anti-isomerism or a mixture thereof, an ester, a pharmaceutically acceptable salt, a prodrug, or a solvate thereof.

2. The compound described in Claim 1 wherein X is N.

3. The compound described in Claim 1 wherein R^1 is amino.

4. The compound described in Claim 1 wherein R^2 is hydrogen or optionally substituted lower alkyl.

5. The compound described in Claim 1 wherein R^2 is lower alkyl optionally substituted with halogen.

6. The compound described in Claim 1 wherein R^3 is hydrogen.

7. The compound described in Claim 1 wherein R^4 is hydrogen, optionally substituted lower alkyl or an optionally substituted N-containing heterocyclic group.

8. The compound described in Claim 7 wherein R^4 is hydrogen, lower alkyl optionally substituted with amino, lower alkylamino or hydroxy(lower) alkylamino, or an optionally substituted 4- to 6-membered N-containing saturated heterocyclic group.

9. The compound described in Claim 1 wherein R^5 is hydrogen.

10. The compound described in Claim 1 wherein the wavy line means syn-isomerism.

11. The compound described in Claim 1 wherein X is N; R^1 is amino; R^2 is hydrogen or optionally substituted lower alkyl; R^3 is hydrogen; R^4 is hydrogen, optionally substituted lower alkyl or an optionally substituted N-containing heterocyclic group; R^5 is hydrogen; and the wavy line means syn-isomerism.

12. The compound described in Claim 11 wherein X is N; R^1 is amino; R^2 is hydrogen or lower alkyl optionally substituted with halogen; R^3 is hydrogen; R^4 is hydrogen, lower alkyl optionally substituted with amino, lower alkylamino or hydroxy(lower)alkylamino, or an optionally substituted 4- to 6-membered N-containing saturated heterocyclic group; R^5 is hydrogen; and the wavy line means syn-isomerism.

13. The compound described in Claim 12 wherein X is N; R^1 is amino; R^2 is hydrogen, $-CH_3$, $-CH_2F$, $-CH_2CH_3$ or $-CH_2CH_2F$; R^3 is hydrogen; R^4 is hydrogen, $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-(CH_2)_3NH_2$, $-(CH_2)_3NHCH_3$, $-(CH_2)_3NH(CH_2)_2OH$, azetidinyl, pyrrolidinyl or piperidyl; R^5 is hydrogen; and the wavy line means syn-isomerism.

14. The compound described in Claim 13 wherein X is N; R^1 is amino; R^2 is hydrogen, $-CH_2F$ or $-CH_2CH_3$; R^3 is hydrogen; R^4 is hydrogen, $-(CH_2)_3NH_2$, $-(CH_2)_3NHCH_3$ or $-(CH_2)_3NH(CH_2)_2OH$; R^5 is hydrogen; the wavy line means syn-isomerism.

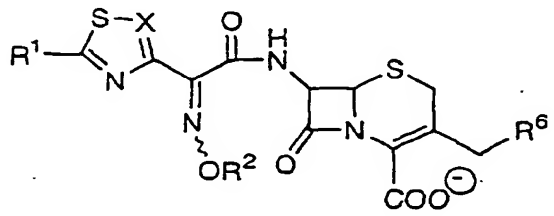
15. The compound described in Claim 14, a pharmaceutically acceptable salt or hydrate thereof wherein X is N; R^1 is amino; R^2 is $-CH_2F$; R^3 is hydrogen; R^4 is $-(CH_2)_3NHCH_3$; R^5 is hydrogen; and the wavy line means syn-isomerism.

16. The compound described in Claim 15 which is a sulfate or a hydrate thereof.

17. The compound described in any one of Claims 1 to 16, which shows an antibacterial activity against Gram-positive bacteria including MRSA and Gram-negative bacteria.

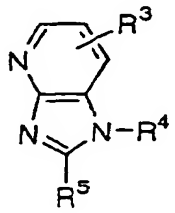
18. The compound described in Claim 17 of which MIC_{50} value against MRSA is 50μg/ml or less.

19. A method for preparing the compound described in any one of Claims 1 to 18, which comprises reacting a compound of the formula(V):



(V)

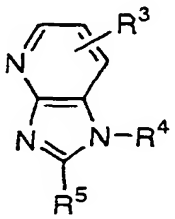
wherein R^6 is a leaving group and the other symbols are the same as defined above, an ester, or a salt thereof with a compound of the formula(IV):



(IV)

wherein each symbol is the same as defined above, followed by optional deprotection.

20. A compound of the formula(IV):



(IV)

wherein each symbol is the same as defined above.

21. The compound described in Claim 20 wherein R^3 is hydrogen; R^4 is - $(CH_2)_3NR^aCH_3$ wherein R^a is H or an amino-protecting group; and R^5 is hydrogen,

22. A pharmaceutical composition which contains the compound described in any one of Claims 1 to 18.

23. A composition for use as an antibacterial agent which contains the compound described in any one of Claims 1 to 18.

24. A method for preventing or treating bacterial infectious diseases, which comprises administering the compound described in any one of Claims 1 to 18.

25. Use of the compound described in any one of Claims 1 to 18 for preparing a composition for use as an antibacterial agent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/06562

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07D519/00, 471/04, A61K31/546, A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07D519/00, 471/04, A61K31/546, A61P31/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS (STN), REGISTRY (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y A	US, 5281589, A (Cheil Foods & Chemicals, Inc.), 25 January, 1994 (25.01.94), especially, see EXAMPLE 19,23, etc. & WO, 92/22556, A1 & EP, 589914, A1 & JP, 7-501311, A	1-14,17-19, 22,23,25 15,16,20,21
Y X A	Kim, Oak K. et al"Synthesis and structure-activity relationship of C-3 quaternary ammonium cephalosporins exhibiting anti-MRSA activities",Bioorg. Med. Chem. Lett., Vol.7, No.21, (1997), p.2753-2758, especially, see Table 1(6g), etc.	1-14,17-19, 22,23,25 20 15,16,21
Y A	JP, 6-41149, A (Toyama Chemical Co., Ltd.), 15 February, 1994 (15.02.94) (Family: none)	1-14,17-19, 22,23,25 15,16,20,21
A	EP, 113965, A2 (ICI PHARMA), 25 July, 1984 (25.07.84) & US, 4547573, A	1-23, 25
X	US, 5719306, A (G. D. Searle & Co.), 17 February, 1998 (17.02.98)	20

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 February, 2000 (14.02.00)	29 February, 2000 (29.02.00)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/06562

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& EP, 804427, A1 & JP, 10-512848, A	
X	JP, 9-165371, A (SANKYO COMPANY, LIMITED), 24 June, 1997 (24.06.97) (Family: none)	20
X A	EP, 680967, A1 (Roussel-UCLAF), 08 November, 1995 (08.11.95) & US, 5635485, A & JP, 8-53489, A	20 21
X	EP, 682024, A1 (Hoechst A.-G.), 15 November, 1995 (15.11.95) & US, 5739147, A & JP, 7-330767, A	20
X	EP, 400974, A2 (Merck and Co., Inc.), 05 December, 1990 (05.12.90) & US, 5332744, A & JP, 3-95181, A	20
X	WO, 94/22859, A1 (Bayer A.-G.), 13 October, 1994 (13.10.94) & EP, 690861, A1 & JP, 8-508268, A	20
X	JP, 5-331149, A (EISAI CO., LTD.), 14 December, 1993 (14.12.93) (Family: none)	20
X	JP, 5-201991, A (DAINIPPON PHARMACEUTICAL CO., LTD.), 10 August, 1993 (10.08.93) (Family: none)	20
X	EP, 497659, A1 (Laboratorios del Dr. Esteve, S.A.), 05 August, 1992 (05.08.92) & US, 5382586, A & JP, 4-312584, A	20
X	EP, 461040, A1 (Roussel-UCLAF), 11 December, 1991 (11.12.91) & US, 5389634, A & JP, 4-235974, A	20
X	EP, 434038, A1 (Takeda Chemical Industries, Ltd.), 26 June, 1991 (26.06.91) & JP, 4-120079, A	20
X	EP, 420237, A1 (Eisai Co., Ltd.), 03 April, 1991 (03.04.91) & US, 5506238, A & JP, 7-224059, A	20
X	JP, 2-48587, A (YAMANOUCHI PHARMACEUTICAL CO., LTD.), 19 February, 1990 (19.02.90) (Family: none)	20
X	EP, 260613, A2 (Searle, G. D., and Co.), 23 March, 1988 (23.03.88), & US, 4804658, A & JP, 63-88182, A	20
X	WO, 97/29748, A1 (Bristol-Myers Squibb Co.), 21 August, 1997 (28.08.97), & US, 5846990, A & EP, 921800, A1	20
X	WO, 98/6720, A1 (Eisai Co., Ltd.), 19 February, 1998 (19.02.98), & AU, 9737849, A1 & EP, 934941, A1	20
X	WO, 96/12703, A1 (G. D. Searle and Co.), 02 May, 1996 (02.05.96),	20

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INTERNATIONAL SEARCH REPORT

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& US, 5635514, A	
X	WO, 95/16687, A1 (Abbott Laboratories), 22 June, 1995 (22.06.95), & US, 5486525, A & EP, 734386, A1	20
X	US, 5334598, A (Merck and Co., Inc.), 02 August, 1994 (02.08.94), & WO, 94/21255, A1	20
X	WO, 92/6086, A1 (Janssen Pharmaceutica NV.), 16 April, 1992 (16.04.92), & AU, 9185067, A1	20
X	WO, 91/13070, A1 (Boehringer Mannheim GmbH, Fed. Rep.), 05 September, 1991 (05.09.91), & DE, 4005970, A1	20
X	US, 4002623, A (Pfizer Inc.), 11 January, 1977 (11.01.77) (Family: none)	20
X	US, 35851999 A (Merck and Co., Inc.), 15 June 1971 (15.06.71) (Family: none)	20

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 24
because they relate to subject matter not required to be searched by this Authority, namely:

The subject matter of claim 24 relates to a method for treatment of the human body by therapy.

2. ☒ Claims Nos.: 20
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

See extra sheet.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

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Continuation of Box No.I of the continuation of first sheet (1)

The Compounds represented by the formula (IV) given in claim 20 have the imidazo[4,5-b]pyridine ring structure alone as the skeleton in common and carry variable groups as the most part of the structure thereof.

There had been known prior to the present application a great number of compounds having such a simple skeleton as the one described above. Namely, the compounds represented by the formula (IV) are structurally characterized by combinations of a plural number of variable groups attached to the above skeleton. However, these variable groups are not structurally specified in the terminal parts and involve "substituted ones".

Thus, the structural characteristics and scope of the compounds represented by the formula (IV), are extremely unclear.

Such being the case, the International Search could not be completely effected on claim 20. Therefore, the Search had been performed some of the compounds represented by the formula (IV) given in claim 20 on the basis of the compounds particularly described in Examples in the specification.

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